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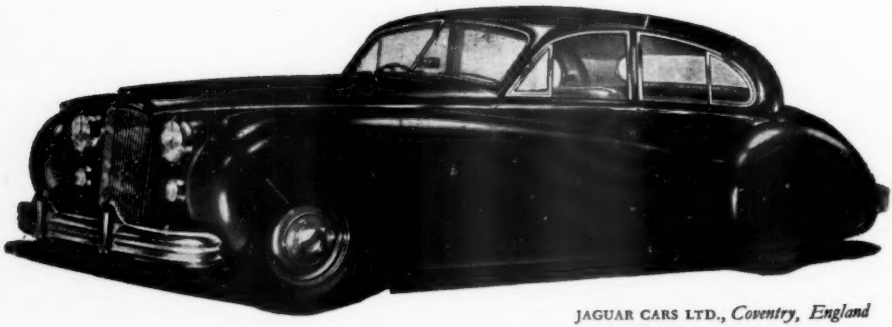

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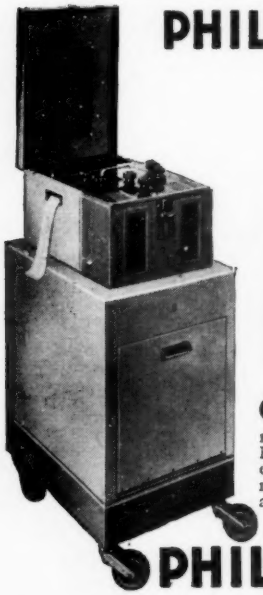

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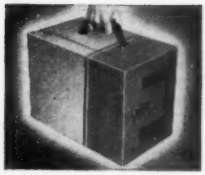

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[*February* 6, 1953]

SYMPOSIUM ON HEARING TESTS AND THEIR SHORTCOMINGS [*Abridged*][1]

Wing Commander P. F. King:

Some Imperfections of the Free-field Voice Tests

Introduction.—The free-field voice tests involve:

(*a*) the conversational voice, and (*b*) the whispered voice as a means of determining the auditory acuity.

In testing with the conversational voice, the distance at which the patient can hear and repeat speech at a conversational level is measured; custom has it that the normal ear can hear at a range of 20 feet. It is doubtful if an examiner speaking always in the same room can constantly maintain the same level for speech; it is certainly a test that does not bear comparison between different examiners.

The use of the conversational voice requires nothing other than one person to speak and provides information concerning a patient's ability to hear speech.

Like the test with the whispered voice, the conversational voice test is easy to perform, quick and convenient, requires no technical assistance and can be used anywhere. Unlike the whisper, it has a use in cases of very advanced deafness.

The whispered voice.—A "whisper" is speech produced on expiration without the vibration of the vocal cords. Normally a "forced whisper" is used which is produced by whispering with the residual air after expiration.

There is no doubt that the normal ear is able to hear whispered sibilants further than low tone words; in practice sibilant phonetic sounds are some 10 decibels louder than others.

In the whisper test tone and pitch variations are practically eliminated and it is easier to maintain a relatively uniform intensity. With the same voice testing the same patient under the same conditions, a *relative* change in the hearing may be assumed to be *factual*.

The weaknesses of the test are:

I. The failure to standardize the technique of giving the test.—We have attempted to standardize the performance of the test throughout the R.A.F. Masking is as important in testing monaural hearing in this as in other tests of auditory acuity. Numbers are easier to hear and comprehend than words; the use of numbers alone limits the test material. We use meaningful words of both high and low frequency content, but it is not known in what proportion the words should be mixed.

II. The inability to control absolutely the pitch and intensity of a whisper is associated with such factors as differences in timbre and quality due to overtones, and to accent and inflection. The inability to control the pitch and intensity of a whisper may be influenced by the ambient noise.

We attempted to determine:

(*a*) the degree of variability between different examiners, and

(*b*) the degree of variability in the intensity of a whisper in any one examiner.

Four otologists accustomed to giving the forced whisper test spoke six words of a testing list under extremely quiet conditions. The loudness of the words was measured in terms of the relative sound pressure levels at 2½ feet from the source of sound.

Table I shows the relationship between the sound pressure recorded for the quietest and loudest word of each examiner, and the pressure ratios. The difference between the pressure of the quietest word and that of the loudest word throughout the test was 28 decibels or a ratio of 1 : 25.

TABLE I

	Quietest word Db.	Loudest word Db.	Pressure ratio
Otologist No. 1	36	50	1 : 5
Otologist No. 2	44	60	1 : 6
Otologist No. 3	34	44	1 : 3
Otologist No. 4	32	46	1 : 5

Sound pressure relative to 0·0002 dynes/sq.cm.

[1] *See J. Laryng.* (1953) 67, 343.

III. The lack of control of ambient noise.—These tests should be conducted in a quiet room, preferably sound-damped, having an ambient noise level of 50 decibels or less. With an increase in the ambient noise the result may be affected either by distracting the patient with a perceptive loss, or possibly aiding one with a conductive loss.

The average sound pressure level produced in giving the 20 feet forced whisper test was measured under varying conditions of ambient noise level. The background noise was raised for the tester by fitting him with a pair of ear-phones through which a controlled amount of aircraft engine noise was injected. From these tests the pressure ratio of the examiner's voice was found to be approximately 3 : 1 (10 db.) for an ambient noise ratio of 10 : 1 (20 db.).

IV. The different acoustic properties of test rooms.—Factors contributing to this problem depend largely on the structure and contents of the room. In an ordinary room the voice will not decay with distance in accordance with any readily definable law due to the reflection of the sound from the walls, floor, &c. This effect can be illustrated by measuring the decay in sound pressure with distance of the spoken word.

Because of the existence of reflections similar results may not be obtained if the line of transmission of the sound is reorientated. Any change in the content of a room will change its transmission characteristics.

The sound intensity at any given distance from a speaker's voice may not be the same for rooms which have different contents and which are of different proportions.

The average sound pressure for a whisper at 2½ feet under very quiet conditions is about 45 decibels; this is a level of some 10–15 decibels below that of the ambient noise of an ordinary room. The test with the whisper therefore gives information not of the sound levels at which the subject hears but of his capacity to interpret speech.

For the accurate measurement of hearing the voice and the whispered voice have but little scientific value. From the clinical standpoint they have a use under limited conditions.

The ability to hear speech is of great concern to the deafened patient. The ability to interpret speech correctly, often under circumstances of stress, is also a condition of many occupations.

In America, the Committee on Hearing of the National Research Council in 1948 adopted pure tone audiometry as the means of measuring hearing and based their standards on this technique; the resulting "Scale of Military Economic and Social Competence of Hearing" is of use to any organization which requires a knowledge of the hearing acuity of its members.

In the future, speech audiometry will probably be used as the basis for hearing standards, and this will be the ideal. Until then, with the impending standardization of pure tone audiometry, some standard of hearing should be achieved by mutual agreement.

Dr. M. R. Dix and Dr. J. D. Hood (Otological Research Unit, Medical Research Council, National Hospital, Queen Square, London):

Modern Developments in Pure Tone Audiometry and Their Application to the Clinical Diagnosis of End-organ Deafness

In recent years the clinical value of loudness recruitment tests in the differential diagnosis of perceptive deafness has come to be widely recognized.

At the same time very little regard appears to have been paid to the physiological principles which underlie the mechanism of the phenomenon itself. Serious uncertainties have, on this account, arisen concerning the relative values of the various testing techniques which are in common use, and even the diagnostic status of the phenomenon itself has been called in question.

In this respect the phenomenon of adaptation plays a vital part and can easily be shown to bring about the abolition or reversal of recruitment if incorrect testing techniques are employed (Hood, 1950; Hallpike and Hood, 1951).

The nature of some of the errors which arise through incorrect testing procedures is illustrated in Fig. 1.

On the left is a conventional graphic representation of loudness recruitment as it is typically encountered in a case of unilateral end-organ deafness. The phenomenon is best revealed by means of the alternate binaural loudness balancing procedure of Fowler. The essential feature of this test is that tones of abrupt onset and short duration should be applied to each ear alternately. The vertical and horizontal scales of the graph refer to sound intensities applied respectively to the normal and affected ears of the subject. The dotted line AB passing through the origin is carried through a series of intensity points which give equal sensations of loudness in the two ears of a normal subject. Since the hearing is equal in the two ears the angle of the line is 45 degrees. The uninterrupted line CD passes through the equal loudness points of an abnormal subject suffering from unilateral end-organ deafness. The deafness at threshold is 30 decibels. It will be seen that full recruitment of loudness is attained at the point X, at which equal intensities, 60 decibels, give equal sensations of loudness in the two ears. It will further be seen that the loudness range covered in the case of the good ear by the intensity range 0–100 decibels is equivalent to the loudness range covered in the case of the impaired ear by an intensity range of 30–80 decibels. The loudness scale in the affected ear is thus greatly

compressed. This compression may be further exemplified if we consider the projection upon the line CD of the interval 20–40 decibels on the intensity scale for the normal ear. This projection is covered by a smaller interval, 40–50 decibels, on the intensity scale for the affected ear. This compression of the loudness scale in the impaired ear has, as its inevitable corollary, a corresponding reduction of the intensity difference limen.

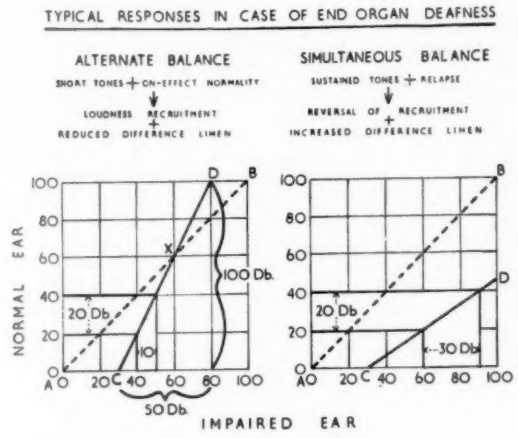

FIG. 1.

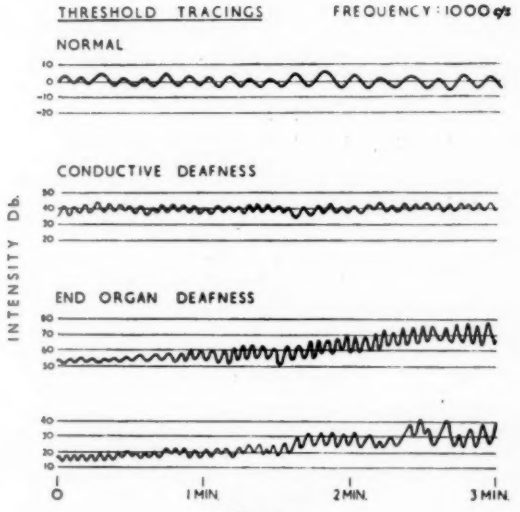

FIG. 2.

The right-hand graph of Fig. 1 depicts the results obtained in the same subject when the loudness balance test is carried out with sustained tones applied to both ears simultaneously. Here it will be seen that the angle of the uninterrupted line CD, instead of inclining towards the line AB, deviates from it, indicating a reversal of loudness recruitment. In this case the projection upon the line CD of the interval 20–40 decibels on the intensity scale for the normal ear is matched by a greater interval, 50–90 decibels, on the intensity scale for the affected ear. In other words, the loudness scale for the affected ear is expanded instead of being compressed. As a corollary, the difference limen under these conditions for the affected ear is increased. This reversal of recruitment with increase of the

difference limen is thought to be due to pathological adaptation occurring in the affected sense organ. The results obtained with the alternate loudness balancing procedure using short tones of abrupt onset in a case of unilateral end-organ deafness may be summarized again as follows: As the stimulus intensity is increased, normal loudness sensations are initiated in the affected ear. This depends upon the capacity of the affected end-organs to respond normally to the short tones of abrupt onset. This effect has been termed "on-effect normality", and constitutes the basis of the loudness recruitment phenomenon. With it the difference limen becomes reduced. If the loudness balancing procedure is carried out with sustained tones "on-effect normality" is replaced by pathological adaptation with reversal of loudness recruitment and an increase of the difference limen.

Adaptation also exerts an important influence at threshold intensities. By coupling the attenuator control of an audiometer to an ink recorder by means of a rack and pinion mechanism the threshold traces shown in Fig. 2 were obtained. It is shown in the upper two tracings that with normal ears or in conductive deafness in which pathological adaptation (relapse) is absent, the traces do not vary. The lower two tracings show how in end-organ deafness there is, on the contrary, a progressive rise of the threshold level. The amplitude of the tracing (a measure of the difference limen), moreover, increases progressively with time. Relapse, therefore, occurs even at threshold intensities giving rise to the reversal of loudness recruitment as indicated by this increase in the difference limen. An important application of this finding is the design of the switching mechanism used for pure tone audiometers. Fig. 3 illustrates audiograms taken using different techniques. In the first (dotted lines) a switch was

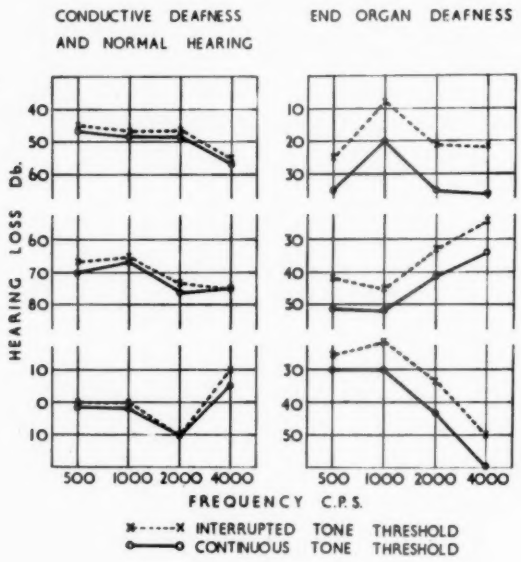

FIG. 3.

used with a rapid build-up time of 30 millisecs. In the second (continuous lines) a method was used in which the intensity was increased continuously at a rate of 2 decibels per sec. until the sound was just heard. It is shown that in cases of normal hearing or conductive deafness there is very little difference in threshold using either technique. In end-organ deafness, on the other hand, the difference is considerable.

There is, at the moment, no degree of standardization in the manner in which the onset of the tone is controlled in any of the commercial audiometers and they appear to vary greatly. From the above results it seems likely that the lack of agreement in audiograms taken with different instruments may be due not so much to differences in calibration as to differences in technique of tonal interruption. The tests described provide, as shown in Fig. 3, the basis of a simple and valuable clinical audiometric test, revealing as they do such marked differences in response between end-organ and conductive deafness.

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Mr. R. S. Dadson (National Physical Laboratory, London):

Some Possible Sources of Error in Audiometry and Their Remedies

Most of the uncertainties or complications arising in audiometry to which reference has been made by previous speakers in this symposium have been of the kind due to physiological or clinical factors which may be present in cases of impaired hearing. There are, however, a number of limitations met with in the use of audiometers which are purely instrumental (or acoustical) in nature and which fall within the scope of a physical laboratory. The object of the present paper is to discuss some of these physical limitations and, where practicable, to consider ways in which improvement may be brought about. We shall not here be concerned specifically with possible defects of construction, such as errors in the frequencies of the tones provided, or in the attenuator readings, and so on, although defects of this nature, especially perhaps in the attenuator readings for low values of hearing loss, have been by no means uncommon. They can, however, be reduced to negligible proportions with care in manufacture, and for the present purpose we shall for simplicity assume that we are considering a properly constructed instrument.

Importance of the reference threshold.—There is little doubt that one of the principal obstacles to accurate audiometry has been the lack of general agreement on the reference zero for the calibration of the scale of hearing loss. This has probably been accentuated by the lack of adequate calibration facilities. The reference zero should evidently correspond to the threshold of hearing of persons free from any form of hearing impairment but there has in the past been no real agreement as to the threshold values at different frequencies. The very diverse information available in 1933 was assessed in a classic paper by Sivian and White (1933), but some later surveys in the U.S.A. (National Health Survey, 1938; Steinberg *et al.*, 1940*a* and *b*) gave results in marked disagreement with Sivian and White's conclusion. The results of one of these surveys (National Health Survey, 1938) forms the basis of the standards for the calibration of audiometers which are understood to be in use at present in the U.S.A., but a study of the records of this work (Steinberg *et al.*, 1940*a* and *b*) leaves some doubt as to whether the experimental conditions adopted were sufficiently definite or repeatable for the purpose of a basic standard.

The impetus to develop proper standards of calibration for audiometers in Great Britain came largely from two sources; on the one hand from this Section of Otology on whose initiative the British Standards Institution took the matter up just before the war, and on the other hand from the Electro-Acoustics Committee of the Medical Research Council which was concerned with improvement in audiometric standards concurrently with its work on the specification of the national hearing aid. At the instance of these bodies a programme of experimental work was undertaken at the National Physical Laboratory in the course of which a thorough investigation was made of the threshold of hearing by earphone listening on a group of about 100 otologically normal subjects confined to the age limits 18–25 years which had been recommended by the Electro-Acoustics Committee, 1947. This work has been described in detail elsewhere (Dadson and King, 1952) and a further investigation on 500 subjects in the same age group has recently been carried out at the Central Medical Establishment of the R.A.F. (Wheeler and Dickson, 1952). These two investigations, in both of which great care was taken over the accurate specification of all the physical factors involved, gave results in very close agreement. The combined data have been accepted by the British Standards Institution Committee concerned as the basis for a British Standard which is now nearly ready for issue, and which it is hoped will go far towards the desired aim of complete uniformity in the calibration of audiometers in the United Kingdom. Opportunity is also being sought for further discussion of the question on international lines in order to widen the basis of agreement as far as is practicable.

Effects of earphone-to-ear coupling.—Having arrived at a satisfactory basis for the calibration of a pure tone audiometer, there remain other sources of uncertainty in use, chief among which are effects due to variability in the coupling between the earphone and the subject's ear. These are of two general kinds, affecting mainly the low and high frequency tones respectively. Leakage of sound resulting from the imperfect seal between the earcap and ear has the effect of reducing the sound transmitted to the ear drum at low frequencies, due both to loss of sound through the leak and to variation in the actual performance of the receiver consequent on the variation in the acoustical impedance imposed upon it. These effects vary from one individual to another since they depend on the configuration of the external ear, and also depend on the force with which the earphone is applied. Over the higher part of the frequency range the sound reaching the ear drum may be affected by wave motion in the cavity formed by the ear and earcap. This effect is again dependent on the shape and volume of the individual ear and on the force of application of the earphone.

Insufficient data is available to indicate precisely the range of variability due to these causes. Some measurements at the National Physical Laboratory show that, for a given pattern of earphone and a definite force of application, the sound pressure reaching the ear drum may vary, as between individuals, by the order of 5 to 10 decibels on either side of the mean for frequencies below 500 c/s and above 4,000 c/s. Over the intermediate frequency range the degree of variability is reduced perhaps to the region of ± 3 db. In order to keep these effects to a minimum it is desirable that the earphone should be applied with a reasonably constant force, for which the value 500 grammes weight is

suggested. The use of a calibrated headband, with the load balanced by a dummy earphone applied to the ear not under test, seems to be the simplest means of achieving this state of affairs for ordinary clinical applications. The design of earphones for use with audiometers deserves further study with a view to reducing the effects already mentioned, but there appears to be no easy solution to the problem.

Limitations due to bone-conducted sounds.—It is evident that the sound from an earphone impinging on an area of bone surrounding the ear canal, may cause transmission by bone conduction as well as by the normal air-conduction path. This effect may be of importance in the case of subjects with fairly severe air conduction loss, but substantially normal hearing by bone conduction. A limited range of measurements at the National Physical Laboratory has indicated that an airborne sound intensity in the region of 110 db. above normal threshold, produced by the usual type of external audiometer earphone, may give rise to mastoid bone vibration varying from some 20 to 60 db. above the bone-conduction threshold over the frequency range 125 to 2,000 c/s. A more detailed account of these measurements has been published in the report of the Electro-Acoustics Committee of the M.R.C., 1947. The figures were, however, obtained on normal subjects and complications may arise in the case of some subjects with severe conductive deafness who may conceivably be more than normally sensitive to bone-conducted sound on account of the well-known occlusion effect. The tests showed that the degree of bone conduction was reduced when using an insert-type earphone, so that the use of such earphones may be worth consideration for some applications where it may be specially desirable to reduce bone-conduction interference.

Bone-conduction audiometry.—We have, so far, considered the standardization of the level of *airborne* sound supplied by the earphone of an audiometer, but the measurement of bone-conducted sound presents problems of a similar nature on which very little evidence is so far available. It is indeed probable that bone-conduction audiometry has on the whole been much more subject to error and uncertainty that in the case of air conduction. The calibration of a bone-conduction receiver is in essentials quite parallel to the calibration of an earphone. In the latter case it is customary to use an "artificial ear" which is designed, theoretically at least, to impose on the earphone an acoustical impedance similar to that of the average human ear. Similarly, as regards the calibration of bone-conduction receivers the first requirement is an "artificial mastoid" which will present to the receiver the same mechanical impedance as the normal human mastoid process. It will be clear, therefore, that before such an instrument can be devised, measurements of the mechanical impedance of the human mastoid process will be necessary. An investigation of the mechanical impedance of the mastoid processes of 20 subjects has recently been completed at the National Physical Laboratory, using patterns of bone-conduction receiver typical of those employed for audiometers (and also for hearing aids). Consideration has been given to the effects of varying the force of application of the receiver and the area of contact with the mastoid process. The full results of this work, which gives very comprehensive data on the mechanical impedance of the mastoid process, are in course of publication. The results obtained are now being applied to the design and construction of an artificial mastoid for the objective calibration of bone-conduction receivers, which is nearing completion. It is hoped that this work will lead to considerable improvement in a field of measurement in which data has up to the present been almost entirely lacking.

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[*May* 1, 1953]

Discussion on the Management of Soft Tissues in Mastoidectomy (*see J. Laryng.*, 1953, **67**, 457).

Section of Epidemiology and Preventive Medicine

President—Professor ROBERT CRUICKSHANK, M.D., F.R.C.P., D.P.H.

[*May* 15, 1953]

DISCUSSION ON POLIOMYELITIS

Dr. J. Stevenson Logan (Medical Officer of Health, Southend-on-Sea):

Poliomyelitis in Southend-on-Sea in 1952

An outbreak of poliomyelitis in 1952, during which the behaviour of the disease differed from all previous experience may merit comment.

The material for this communication is very complete, since practically all the cases were admitted to one hospital, and diagnosis has been very largely the responsibility of two colleagues, Dr. H. Crosswell and Dr. J. C. Preston, who also saw in domiciliary consultation a number of patients in whom the disease was suspected but not confirmed. All the cases diagnosed as non-paralytic poliomyelitis showed significant changes in the cell and protein content of the C.S.F.

Poliomyelitis was first recognized in Southend-on-Sea in 1912, there was a high incidence in 1926, 1932, 1938; as well as in 1947, 1949 and 1950; it was entirely absent during 1951 and the first half of 1952. The 1952 outbreak was numerically the most important we have ever experienced.

In previous outbreaks careful investigation had never revealed any significant links between cases, although since 1947 there have been some recognizable geographical groupings of notifications. Before 1952 we had never met multiple cases in one family.

Table I analyses for each succeeding period of four weeks the cases according to dates of onset.

TABLE I.—CLASSIFICATION BY AGE, SEX AND TYPE

PERIOD		0-5		5-10		10-15		15-20		20-25		25-30		30-35		over 35		TOTALS			
		M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M+F	CASES
24.6.52 - 21.7.52	P	1	-	2	2	-	-	-	-	-	-	-	-	1	-	-	-	4	2	6	10
	NP	-	-	2	1	-	-	-	-	-	-	-	-	-	-	-	-	3	1	4	
22.7.52 - 18.8.52	P	1	1	1	1	-	-	-	-	-	-	-	-	-	-	-	-	2	2	4	14
	NP	2	1	1	2	2	1	-	-	-	-	-	-	-	1	-	-	5	5	10	
19.8.52 - 15.9.52	P	1	1	3	3	1	1	1	-	-	1	2	1	-	1	-	-	8	8	16	28
	NP	2	2	3	-	-	1	1	-	-	-	2	1	-	-	-	-	8	4	12	
16.9.52 - 13.10.52	P	2	-	2	2	-	-	-	-	-	-	-	-	-	1	-	-	4	3	7	25
	NP	5	2	5	5	-	-	-	-	-	-	1	-	-	-	-	-	11	7	18	
14.10.52 - 10.11.52	P	2	-	-	1	-	1	-	-	-	-	-	-	-	-	-	1	2	3	5	14
	NP	-	-	7	1	-	1	-	-	-	-	-	-	-	-	-	-	7	2	9	
11.11.52 - 8.12.52	P	-	1	-	1	-	-	-	-	-	-	-	-	1	-	-	-	1	2	3	6
	NP	1	-	1	1	-	-	-	-	-	-	-	-	-	-	-	-	2	1	3	
9.12.52 - 31.12.52	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1
	NP	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	1	1	
TOTALS	P	7	3	8	10	1	2	1	-	-	1	2	1	2	2	-	1	21	20	41	
	NP	10	5	19	11	2	3	1	-	-	-	3	1	1	1	-	-	36	21	57	
TOTAL CASES		25		48		8		2		1		7		6		1		98			

P-PARALYTIC NP-NON PARALYTIC

Although male cases (57) outnumbered female cases (41), the incidence of paralysis was practically identical in the sexes; disparity between the sexes was most marked up to 10 years (29 non-paralytic cases among boys and only 16 among girls).

There was relative immunity of the 15 to 25 age group (3 cases only), and even these occurred at the extremes of the group. This contrasts sharply with 1950 when the 15 to 20 group had 4 paralytic cases (3 fatal) but parallels the 1947 experience when only 2 cases occurred in the group 15 to 25.

The clinical features in paralytic cases varied during the outbreak, for example 4 out of 7 cases in Period 4 showed mild or moderate bulbar involvement while Period 6 provided 2 fatal cases from 3 notifications (Table II).

TABLE II.—CLINICAL FEATURES IN PARALYTIC CASES

Period	No. of cases	Type			Degree				Ages of fatal cases
		Respiratory	Bulbar	Spinal	Mild	Moderate	Severe	Fatal	
1	6	1	—	6	2	3	—	1	6
2	4	—	1	3	2	2	—	—	
3	16	3	3	13	8	3	2	3	26 9 13
4	7	—	4	4	4	3	—	—	
5	5	1	1	4	3	1	—	1	36
6	3	1	1	3	1	—	—	2	31 7

Evidences of infectivity were striking. The disease was first centred in Hamlet Court Road School comprising an infant and a junior department, each structurally separate but within the same curtilage. The first case, a boy, attended the Junior Department; shortly before he became ill, his cousin who attends the Infant Department, and with whom he was in house contact, had an ill-defined upper respiratory illness. Case No. 2 who came from the Infant Department was friendly with this same cousin of No. 1. Case No. 3 came from the Infant Class II, and Cases 4 and 5 from Infant Class IV. Case 6 came from another school but she and her family had multiple contacts with a child from the Hamlet Court Road Infant School, who had himself suffered from an ill-defined illness characterized by persistent and intense headache, which may very well have been an abortive poliomyelitis.

The sister and the mother of a child in the Junior Department developed poliomyelitis very shortly after going on holiday. Case 10, whose own children attended a private school, lived next door to a family where there were several children, one of whom attended the Hamlet Court Road Infant Department. Case 14 was the mother of a child in the Junior Department, and Case 8 a contact of a child in the Infant Department, as was Case 29.

We recognized that district spread and school spread were occurring simultaneously and eventually established some kind of linkage between infected households and infected districts for Cases 7, 9, 11, 16, 21, 30, 33, 47, 55, 56, 67 and 97, as well as for an unfortunate visitor who contracted the disease subsequent to her return home.

To distinguish district spread from case-to-case infectivity is difficult as is shown by events in a comparatively isolated area of Shoeburyness, a district which remained free from poliomyelitis until September 1, when a boy who lived in No. 15 (Fig. 1) sickened; three days after he fell ill his sister almost certainly developed abortive poliomyelitis. At No. 44 a young married student school teacher, Mrs. N., who had no known contact with the children at No. 15, began to be ill on September 4 as did her brother between September 4 and 6. Her husband, a corporal at Chatham, who had been on holiday with her until August 30 and visited his home again on September 5/6 also developed poliomyelitis on September 14. Her mother was a school clerk who also taught music pupils in her own home. When Mrs. N. fell ill, Mrs. H. at No. 31 helped to nurse the patient until her removal to hospital on September 9. On September 12 V. H., daughter of Mrs. H. and pupil of Mrs. N.'s mother, sickened and died a few days later. In addition to the contacts at No. 44, V. H. had contact with the children at No. 15.

Finally on September 21, a 21-month-old child at No. 14, who was said to have no contact with the other cases, developed poliomyelitis. Simultaneously with these events a youth in another part of Shoeburyness developed severe paralytic poliomyelitis on September 3 and another non-paralytic case which had no discernible connexion with any other developed on September 20.

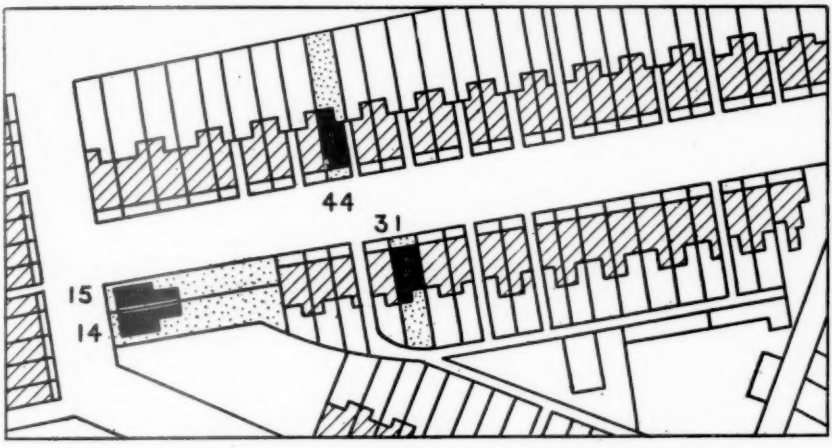

FIG. 1.—Street plan to show location of infected households in Shoeburyness.

Table III deals with multiple cases, representing nearly a quarter of the total notified cases, occurring in the same household. September, which is included in four-week periods Nos. 3 and 4, produced the largest number of multiple cases, which, however, continued to occur until the end of November.

TABLE III.—MULTIPLE CASES IN SAME HOUSEHOLD

Case No.	Age	Onset	Result
17	8	23.7.52	N.P.
19	3	5.8.52	N.P.
22	14	8.8.52	N.P.
31	7	1.9.52	P.
36	6/12	6.9.52	N.P.
41	20	4.9.52	P.
43	17	4–6.9.52	N.P.
46	26	14.9.52	P.
48	5	15.9.52	P.
53	3	21.9.52	N.P.
49	6	14.9.52	N.P.
58	3	23.9.52	N.P.
62	7	24.9.52	N.P.
63	2	25.9.52	N.P.
64	1	25.9.52	P.
65	5	29.9.52	P.
85A	4	20.10.52	P.
85	7	4.11.52	N.P.
88	11	7.11.52	N.P.
87	36	6.11.52	Died (Bulb.)
93	4	20.11.52	P.
94	1½	25.11.52	N.P.
95	7	30.11.52	P. Died

Table IV gives particulars of cases which seem to be linked.

TABLE IV.—ASSOCIATED CASES

Case No.	Age	Onset	Remarks
45	6	10.9.52	Cousin Contact 8.9.52
44	4	12.9.52	,, 9.9.52
52	3	15.9.52	Contact No. 45 10.9.52
17	8	23.7.52	
19	3	5.8.52	
22	14	8.8.52	
20	7	11.8.52	
		T. INFANTS SCHOOL	
74	5	9.10.52	Class VII
83	5	24.10.52	Class VII
96	6	29.11.52	Class III
		R.A. SCHOOL	
75	8	12.10.52	Class VI Junior
81	1	25.10.52	Contact
86	9	2.11.52	Class III Junior
		S.M. SCHOOL AND CHURCH	
78	8	13.10.52	Class IV
82	6	27.10.52	Class VII. (His sister was in Class IV)
87	36	6.11.52	School and Church
88	11	7.11.52	

The Hamlet Court Road School series and those associated with district spread in Westcliff are not included, neither are all the instances of possible association between patients suffering from poliomyelitis, only those least open to doubt have been selected.

Some impressions may be of interest. The most striking has been the frequency with which school teachers have been reported in our investigations. The father of Nos. 17 and 22 was a school teacher and No. 19 was daily minded at his home. The father of No. 6 is a school teacher; No. 37 had two school teacher sisters. No. 41 was a student school teacher; the father of No. 85 and No. 85a was a headmaster; not only did he live in the Westcliff area but his school, which his children attended, served the area of Shoeburyness which was first affected; the mother of No. 41 was his school clerk, and the mother of No. 42, a dining room attendant at the school. The husband of No. 87 and the father of No. 88 was a school teacher, and three days after the first case occurred in his household, a child in the school where he is employed developed poliomyelitis. The sister of No. 50 was also a school teacher.

In marked contrast we know of no cases occurring in the family of a medical practitioner, and there is only a very tenuous link between No. 26 and a nurse employed at the Isolation Hospital.

In seeking to find linkages between cases one must always remember that to demonstrate the opportunity for infection to occur is not proof of it happening, for there must be some point at which chance enters in. However, to find that a child, while sickening for poliomyelitis is taken to a wedding reception in a neighbouring village attended by a girl from another part of the town, in whose school class there is the sister of a child who later develops poliomyelitis is, to invite speculation.

In a quarter of our cases there was a food handler in the household but we found nothing which suggested that food handlers played any part in the spreading of the disease. A high proportion of food handlers is to be expected in the population of a resort.

As regards diagnosis, one must pay tribute to Dr. H. Crosswell, Physician Superintendent of the Isolation Hospital, and my Deputy, Dr. J. C. Preston, who is in charge of the hospital in Dr. Crosswell's absence. Between them they saw all of the cases discussed here, together with many more where they did not diagnose poliomyelitis. There was only one instance in which a provisionally negative diagnosis required alteration. This shows that those who lightly dismiss the possibility of distinguishing non-paralytic cases from other patients presenting with minor and obscure illnesses do less than justice to the value of experience coupled with careful systematic clinical examination. We were particularly indebted to Dr. R. Pilsworth, Director of the Public Health Service Laboratory, situated at the Isolation Hospital, for the examination of the cerebrospinal fluid, which in most instances was completed within two hours of the patient's admission to hospital, irrespective of the time when the admission took place.

A very considerable amount of labour was expended in enquiries. Initially these are best done by an experienced Medical Officer who should give patients' relatives ample opportunity to recollect, and to talk about events connected with the illness. It is useful to record this interrogation almost verbatim, for matters which do not appear relevant during the interview often look very different when notes are worked over later on. Interrogation stimulates the memory and when sanitary inspectors and others make subsequent visits, they often are told of significant happenings which were not immediately recalled.

I cannot say enough about the assistance I have received from my Chief Sanitary Inspector, Mr. R. A. Drake, or his assistant.

Dr. A. P. Goffe (Virus Reference Laboratory, Central Public Health Laboratory, Colindale):

Poliomyelitis: Recent Developments in Laboratory Techniques

Serological types.—Strains of poliomyelitis virus may be grouped into three distinct immunological types, between which little or no cross-immunity can be shown. The National Foundation for Infantile Paralysis of the United States supported the first large-scale typing study in which four University departments co-operated (Committee on Typing, 1951). One hundred strains of virus mainly from North America, but including some from Europe, the Middle and Far East and Australia, were typed using the technique of either cross-immunization and reinfection tests in monkeys or preparation of monkey hyperimmune sera and cross-neutralization tests in monkeys. The type distribution was as follows: resembling the "Brunhilde" prototype strain (Type 1)—85 strains; "Lansing" (Type 2)—12 strains; "Leon" (Type 3)—3 strains. The preponderance of Type 1 was notable, but subsequent surveys using tissue culture methods have given higher proportions of Type 3 strains (Robbins *et al.*, 1951; Riordan *et al.*, 1952; Youngner *et al.*, 1952). All the then known rodent-adapted strains were found to be of the same immunological type (Type 2).

Experiments on pathogenesis.—Recent experiments with cynomolgus monkeys and chimpanzees, both of which resemble the human host in being susceptible to oral infection, have modified the older views on pathogenesis which were largely based on experiments with rhesus monkeys in which the pattern of the experimental disease bears less resemblance to the natural disease. In both the former species virus has been demonstrated in the blood stream either before the onset of paralysis in animals developing paralysis or at the corresponding stage in animals showing the non-paralytic form of the disease (Bodian, 1952*a*,; Horstmann, 1952; Faber *et al.*, 1953). In different experiments virus has been found in the blood between the third and sixteenth days after ingestion, thus preceding or coinciding with the onset of fæcal excretion. It disappeared from the blood stream at the time that antibody first appeared. Most recently virus has been isolated, using the tissue culture technique, from the blood stream of four children in a "family outbreak", one of whom was completely asymptomatic while the other three were between the second and fourth days of an abortive type of illness (Horstmann and McCollum, 1953). There has been much speculation on the origin and significance of this early viræmia. Should it be shown, however, that in order to gain access to the nervous system the virus must pass through the blood stream, then either passively or actively produced antibody might reasonably be expected to block its path.

Passive immunity.—American Red Cross *gamma*-globulin has a high titre of neutralizing antibody against all three types of poliomyelitis virus (Bodian, 1949*a*). Cynomolgus monkeys are protected if injected immediately before or at the same time as oral infection (Bodian, 1952*b*), even after tonsillectomy which greatly increases the rate of paralysis in orally infected animals (Adams *et al.*, 1953). The protective effect of this type of *gamma*-globulin in children was shown last year in the United States (Hammon *et al.*, 1953). A high degree of protection was afforded from the beginning of the second to the end of the fifth week after the injection of 10 ml. of globulin.

Active immunity.—Experiments are now in progress by a number of workers in the United States and in Sweden with the object of producing a safe and effective vaccine, using virus adapted to experimental animals, chick embryos and tissue cultures (Howe, 1952; Salk *et al.*, 1953; Cox, 1953).

Adaptation to mice.—Nine strains all belonging to Type 2 have been adapted to mice by the intracerebral route mostly through monkeys and cotton rats (Bodian, 1949*b*). Many attempts to adapt other strains have been unsuccessful. However, one strain of Type 3 virus (Leon) has been shown to infect mice after direct inoculation into the spinal cord (Li and Habel, 1951). Recently a Type 1 strain (Mahoney) from tissue culture has also been adapted to mice and cotton-rats by the intraspinal technique (Li and Schaeffer, 1953). The MEF-1 strain (Type 2) has been adapted to baby mice which are relatively insusceptible to other mouse-adapted strains (Casals *et al.*, 1951*a*). After repeated intracerebral passages in these animals, brain suspensions were found to yield a satisfactory complement-fixing antigen (Casals *et al.*, 1951*b*).

The complement-fixation test.—A sensitive and economical modification of the original technique has been devised (Le Bouvier, 1953). Table I illustrates results obtained by Dr. Le Bouvier working in

TABLE I.—COMPLEMENT-FIXATION WITH SERA OF POLIOMYELITIS PATIENTS (GATESHEAD, 1952)

Type of case	Time of collection of serum (Days after onset) 1st Specimen	2nd Specimen	CF titres of sera: Serum control	N antigen	EMC antigen	M antigen
PP	4		0	0	0	2
NPP	3	17	0, 0	0, 0	0, 0	(2) 0
NPP	5	40	0, 0	0, 0	0, 0	32, H
PP (fatal)	2		0	16	16	16
PP	3	26	0, 0	0, 0	0, 0	2, 4
PP	7	30	0, 0	0, 0	0, 0	8, 4
NPP	?	?	0, 0	0, 0	0, 0	0, 6
Standard positive serum			0	0	0	16

PP = Paralytic poliomyelitis. NPP = Non-paralytic poliomyelitis.
N = Baby mouse brain antigen (normal control).
EMC = EMC baby mouse brain antigen (inflamed brain control).
M = Poliomyelitis infected baby mouse brain antigen.
H = Hæmolysed serum, test unreadable.

this laboratory with sera from cases occurring during an outbreak of poliomyelitis at Gateshead in 1952. From one patient Type 1 virus has been isolated.

Although the antigen is prepared from a Type 2 strain, positive results may also be obtained in infection with Types 1 and 3 viruses. The amount of fixation sometimes is low and the titre tends to fall after some weeks (Casals *et al.*, 1952). This contrasts with neutralizing antibody which persists for years at high titre (Winsser and Sabin, 1952). A positive complement-fixation reaction may be an indication of recent infection.

Adaptation to hamsters and chick embryos.—The MEF-1 strain has also been adapted to the brain of baby hamsters, in which tissue the highest concentrations of poliomyelitis virus have been found (Moyer *et al.*, 1952). Although of extreme virulence for baby hamsters this line of virus is almost avirulent for monkeys. The hamster line of MEF-1 has been adapted to chick embryos by yolk-sac and allantoic routes (Roca-Garcia *et al.*, 1952; Cabasso *et al.*, 1952). Preliminary work suggests that chick embryo-adapted virus is avirulent for primates, but after feeding to chimpanzees Type 2 neutralizing antibody is formed.

Growth in tissue culture.—Following the original work of Enders many workers have grown poliomyelitis virus in tissue cultures (Enders, 1952). Two techniques have been used widely. *Suspended cell cultures* consist of minced tissue suspended in a nutrient medium in a stoppered flask. Such cultures, slow growing, will support the growth of virus for up to 125 days if the medium is replaced at intervals (Duncan *et al.*, 1953). Tissue from both man and monkeys has been shown capable of supporting the growth of virus, but some tissues give better results (Weller *et al.*, 1952). *Roller tube cultures* are now more extensively used than suspended cell cultures. Tissue is fixed to the side of glass tubes usually by clotted fowl plasma, and the medium is added to the tube which is then incubated in a rotating apparatus inclined to the horizontal about 5 degrees. A rapid growth of new cells occurs consisting of either fibroblasts or epithelial cells, depending on the tissue of origin. Many tissues from man and monkeys support virus growth in these cultures—again with some differences, mainly attributable to the rate of growth of cells or the type of outgrowth formation. Nearly all tissues from human embryos are susceptible, but kidney, skin, testes and uterus from adults have been used successfully (Robbins *et al.*, 1952). From mature monkeys cultures of kidney, muscle and testes are suitable (Ledinko *et al.*, 1952). Cultures of tissues from other species, including rodents, have given uniformly negative results even with rodent adapted strains. In this laboratory most work has been done with cultures of monkey testicle obtained from laboratory animals before they are used for experimental purposes. The growth of virus in susceptible cultures of this sort is accompanied by a degeneration of the outgrowing cells which is clearly visible under the low power of the microscope (*see* Figs. 1 and 2). This effect, referred to as the cytopathogenic effect, and its neutralization by specific serum enable isolation and identification of strains to be carried out on a scale previously precluded by the high cost of experimental animals. Likewise the technique has been used for the precise titration of serum antibody. Other applications include the preparation of type-specific complement-fixing antigens (Svedmyr *et al.*, 1953) and the production of experimental vaccines from infected tissue cultures (Salk *et al.*, 1953). Studies of the amino-acid composition of tissue culture media have shown that *d*-methionine is an essential growth factor for the virus (Brown, 1952).

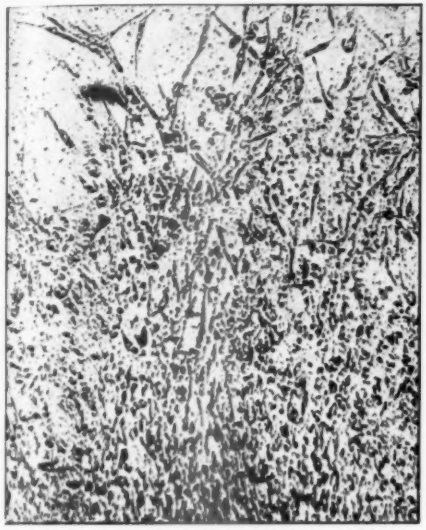

FIG. 1.—Fibroblasts from monkey testicle six days after inoculation with Type 1 poliomyelitis virus (Guildford strain) plus Type 3 antiserum. Cytopathogenic effect. × 80.

FIG. 2.—Fibroblasts from monkey testicle six days after inoculation with Type 1 poliomyelitis virus plus Type 1 antiserum; normal structure. × 80.

The first application of the technique in this laboratory has been in the isolation and typing of strains from England and Wales. For this purpose extracts of stool freed from bacteria by centrifugation have been inoculated into cultures prepared from monkey testicle. Many non-specific degenerative effects due to extraneous material in these extracts make interpretation of the first passage cultures difficult. Therefore, culture fluids collected between the eighth and sixteenth days after infection in the first series are inoculated into a second generation of cultures which are closely watched for cytopathogenic effect. If this occurs fluids from the second generation of cultures are inoculated along with type-specific sera into a third generation. The nine strains so far identified by this technique are indicated in Table II. It remains to be shown whether epidemics are homogeneous

TABLE II.—ISOLATION AND TYPING OF BRITISH STRAINS OF POLIOMYELITIS VIRUS

	Age	Type of case	Area	Date	Virus type
1.	Baby	Bell's palsy	Cardiff	Dec. 1951	3
2.	4½	PP fatal	Gateshead	May 1952	1
3.	20	PP	London	Aug. 1952	3
4.	3	Abortive†	Guildford	Sept. 1952	1
5.	4	Asymptomatic†	Guildford	Sept. 1952	1
6.	6	Asymptomatic†	Guildford	Sept. 1952	1
7.	12 days ..	PP fatal	Aylesbury	Oct. 1952	3
8.	18 days ..	PP fatal	Aylesbury	Oct. 1952	3
9.	Adult ..	Asymptomatic*	Aylesbury	Oct. 1952	3

†Children of paralytic case. *Mother of paralytic case

PP Paralytic poliomyelitis.

or are caused by more than one type. But definite evidence is here presented that both Type 1 and Type 3 contribute to the prevalence of infection in this country.[1]

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[1]Since this paper was given, strains of Type 2 have also been isolated.

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Dr. W. Ritchie Russell:

Recent Developments in Methods of Treatment

Last year Copenhagen experienced an epidemic of poliomyelitis of unusual severity, and we have all read about the dramatic steps taken by Professor H. C. A. Lassen and his staff to deal with the cases which developed respiratory insufficiency, and several members of this Section have visited his clinic. I myself enjoyed the privilege of visiting Professor Lassen to discuss the many problems which his remarkable experience has brought into prominence.

Those who have had experience of treating acute poliomyelitis realize only too well the alarming problems which may develop and which require not only prompt recognition but also highly skilled action if they are to be dealt with effectively.

In the acute stage of the disease it is vitally important first to keep the airways clear, and secondly to provide artificial respiration when required. Close individual and experienced supervision of each patient is necessary if complications are to be recognized and dealt with in time. Professor Lassen had some hundreds of trained nurses to help. Each critically ill patient had a trained nurse constantly at hand, and also a student if necessary to provide positive pressure artificial respiration, while a doctor was within a few yards of the ward and available both day and night to deal with emergencies.

Complicated though Professor Lassen's methods were, they were also simplified by the concentration of patients from a large population into one hospital, so that the difficult cases were treated by those who had plenty of experience of the problems which arise. Special apparatus is of no value without the nurses and junior doctors trained to apply current knowledge and to operate the apparatus.

Recognition of the need for special intervention.—Many cases of paralytic poliomyelitis are relatively comfortable both physically and mentally, and these we watch with thankfulness that they continue to be able to breathe and to swallow.

I shall avoid using the ambiguous term "bulbar" poliomyelitis as much as possible, but we must consider most carefully that type of case which develops paralysis of swallowing. In children, especially, this may be associated with unconsciousness, but even so a wonderful recovery may be expected, if the airways can be kept free. Paralysis of swallowing is a highly dangerous symptom unless it is recognized and treated. A pool of mucus collects in the throat which interferes with breathing, cerebral anoxia develops, consciousness is dulled, the secretions are inhaled and the patient drowns in his own saliva. Relatives, nurses and even doctors, often make the grave mistake of propping up these patients "to help them to breathe", and this simply aggravates the tendency to inhale secretions which cannot be swallowed. Use of a respirator in such circumstances is lethal, as it forces inhalation of the mucus pool.

It is a remarkable fact that a very simple first-aid manœuvre often saves life in these patients. This is simply to turn them into the face-down posture: this should be an immediate first-aid measure applied in the home, and the patient then brought to hospital lying semi-prone on the stretcher. If secretions have already been inhaled and the patient is blue and gravely embarrassed, the foot of the bed or stretcher is raised 18 in. and with the patient prone the chest is sharply squeezed during expiration. In such circumstances fluid pours out of the lungs and mouth as it does out of a half-drowned man, and a dramatic improvement in colour and consciousness often follows. This type of case often has adequate strength in the respiratory muscles if the airways can be kept clear.

Professor Lassen used immediate tracheotomy for this type of gravely ill case, partly to seal off the trachea from the pharynx and partly to facilitate use of the sucker. Over 40% of the cases surviving after his method of treatment required artificial respiration for less than five days, and therefore must fall into the group in which the dominant problem was paralysis of swallowing, and respiratory muscles were not greatly weakened. In this group of Professor Lassen's, there were clearly many, as he himself admits, who might have recovered with postural drainage only, but he feels that it is often safer to do a tracheotomy so that positive pressure ventilation can be applied very quickly should it be needed.

Be that as it may, all are agreed that postural drainage alone if properly carried out will save many lives. Steep head-down tilting should not have to be maintained for long periods, but should be used to achieve extra clearance whenever this seems desirable.

Many of these "drowning" patients give a false impression of having respiratory paralysis, as their muscles become exhausted with struggling to clear mucus from the throat, and it will be appreciated that the degree of respiratory weakness, if any, can only be assessed after the airways have been cleared. If we have the necessary apparatus and know how to use it, we can safely try postural drainage first.

The cases just described are often referred to as pure bulbar cases, and should be clearly distinguished from respiratory insufficiency due to paralysis of intercostal, abdominal muscles, the diaphragm, or any combination of these three. Here there is no paralysis of swallowing but often a progressive reduction in vital capacity which may reach a dangerously low level before the true state of affairs is appreciated. When this critical condition develops, mucus may gather in the pharynx and trachea, not from paralysis of swallowing, but from paralysis of coughing, and the congestion and œdema which develop rapidly with hypoxia. At first sight this clinical picture closely resembles that of the pure bulbar case.

Inspection of the chest and abdomen will usually allow the experienced physician to assess the true state of affairs, and the prone posture may again be used along with manually assisted expiration to clear the airways. Raising the foot of the bed assists diaphragmatic breathing when the abdominal muscles are paralysed, as in this posture the weight of the abdominal viscera provides an expiratory force which is otherwise absent.

When the clinical picture in such a case is clearly due to respiratory paralysis, then prompt measures are required to provide artificial respiration and thus arrest the fatal vicious cycles which quickly occur in prolonged hypoxia. We should aim at recognizing the progressive weakening of respiration long before it becomes dangerous, and the regular use of the spirometer to measure vital capacity is specially useful in this connexion. If the staff are experienced, it seems desirable to provide artificial respiration in the box respirator early in these cases in order to rest weakened muscles, and to avoid the perils of anoxia, but in Copenhagen many such cases were admitted in a gravely ill condition, with fluid in the air passages, and were treated by immediate tracheotomy and positive pressure breathing.

Here it should be explained that artificial respiration may be provided by applying negative pressure to the chest as in a box respirator, or positive pressure to the mouth or cuffed tracheotomy tube as in Professor Lassen's cases. Both methods in skilled hands will keep alive a lot of patients with paralysis of respiration, and we have no easy method of estimating which method saves most lives. I feel that we in this country should continue to use a box respirator for purely spinal cases, but should improve our respirator technique as much as possible. A tracheotomy tube in cases of spinal paralysis provides special problems when it is continued for many months. Most of the 30 or 40 cases remaining now in Professor Lassen's wards have no difficulty in swallowing, but have severe spinal, thoracic, diaphragm or shoulder girdle paralysis, and require artificial respiration for at least part of the day or night. These cases are thus identical with our familiar long-term respirator cases. At this stage, however, they would be much better without their tracheotomy tubes, for they all have a mild infection of the trachea and bronchi, and many have a sucker used to remove secretions every two or three hours. It is hard to see how some of them can be weaned from the tracheotomy tube, for the excessive secretions in the trachea will continue for some days after the tracheotomy tube is removed, and during this period the maintenance of unobstructed artificial respiration in a patient who cannot cough at all will be extremely difficult and sometimes impossible.

The cuffed tracheotomy tube used in Copenhagen renders the patient unable to speak a single word during the critical phase of the disease, and the ethical and psychological factors involved in rendering gravely ill or dying patients incapable of any contact with their relatives or doctors, require careful consideration.

Combined cases.—The worst problems are provided by those patients who have severe paralysis of swallowing, and who, in spite of perfectly free airways, also develop respiratory insufficiency due to spinal paralysis. Here it is necessary not only to keep the airways free by postural drainage or tracheotomy, but to provide artificial respiration as well. This is often a relatively small group but an important one, as the limbs and body are often little paralysed and a good recovery may be secured.

Professor Lassen's method in skilled hands may prove to be the method most likely to succeed in this group, but his actual figures for this type are not available. Many American clinics favour the use of the tank respirator along with tracheotomy in this group. Another method of treatment which may also succeed is to use a tank respirator in which the patient can lie prone or semi-prone. In the assessment of these cases the use of an oximeter, spirometer and perhaps a throat microphone, will all improve the chances of success, and certainly will help to show when artificial respiration is required. Professor Lassen informs me that he has found a rise of blood pressure to be a reliable early sign of CO_2 retention.

All are agreed that the cuirass respirator is inadequate for acute cases with severe respiratory paralysis. Adequate tidal air can be obtained only with the tank-type of respirator or with positive pressure breathing to tracheotomy tube or face mask.

Professor Lassen is experimenting with various types of mechanical apparatus which will continue positive pressure tracheal breathing automatically. It remains to be seen, however, whether the lung alveoli will withstand for indefinite periods the pressure cycles to which these methods subject them.

Teams of experts are required in each hospital admitting polio. The anæsthetist will be an important member of the team, especially if he has had experience of chest surgery, but he should realise that his anæsthetic methods may not always be appropriate to the particular problem. Whoever takes charge of the case must be familiar with all aspects of the disease, so that he can, early on, enlist the most suitable aid from his colleagues.

[At a meeting of the Section of Epidemiology and Preventive Medicine held on October 16, 1953, a paper entitled "The epidemic of poliomyelitis in Copenhagen in 1952" was presented by Professor H. C. A. Lassen and Dr. J. R. Ibsen. It is hoped that a report of this paper will be published in the *Proceedings*, early in 1954.]

Section of Orthopædics

President—H. JACKSON BURROWS, M.A., M.D., F.R.C.S., F.R.A.C.S.

[*June* 8, 1953]

Osteoid-Osteoma

By HENRY L. JAFFE, M.D.
Hospital for Joint Diseases, New York, N.Y., U.S.A.

IT is about twenty years since the concept of osteoid-osteoma of bone began to shape itself in my mind. The idea was stimulated by the study of 5 cases observed in 1933. These were all cases in which there was a lesion in a spongy bone area with the clinical diagnosis of "localized osteomyelitis" or "bone abscess", but in which the tissue submitted for microscopy failed to show evidence of inflammation. Instead, it showed as the significant pathologic feature a nidus-like focus of osteoid and new bone whose removal promptly and permanently abolished the patient's complaints.

Search of the literature (including a number of radiographic atlases) yielded largely negative results. Feeling increasingly that the condition represented something distinctive, I gathered these 5 cases together for publication, formulating the name of "osteoid-osteoma" to characterize the lesion's pathological pattern (Jaffe, 1935).

It was not until 1938 that we realized that an osteoid-osteoma may also develop in relation to the cortex of a bone. This came to light in cases, involving long bones in particular, which were ascribed clinically to "sclerosing non-suppurative osteomyelitis" and "osteomyelitis with cortical bone abscess". Previously we had been puzzled by such cases because of the difficulty of reconciling the clinical diagnosis with the absence of microscopical evidence of inflammation in the bone shavings.

When the next pertinent case presented itself clinically, the surgeon was prevailed upon to do a block resection of the affected area, so that we could study the supposed abscess intact in its setting of thickened cortex. To my surprise, the area supposedly representing the cortical abscess turned out, on histologic examination, to represent the same lesion which, in relation to spongy bone areas, I had designated as osteoid-osteoma. When, through the study of additional cases, it became clear that such cortical lesions likewise belong in the category of osteoid-osteoma, the concept was fully launched (Jaffe and Lichtenstein, 1940). However, the general acceptance of osteoid-osteoma as a clinico-pathologic entity was rather slow, though, sooner or later, various centres have come to accord it recognition.

The osteoid-osteoma lesion.—The osteoid-osteoma lesion evolves slowly, and often gives rise to clinical complaints for many months before its presence is demonstrable in the X-ray picture at all, and even longer before the X-ray picture is reasonably clear-cut. The evolving lesion has two components: (1) the core or nidus-like focus (the osteoid-osteoma proper), and (2) the reactive perifocal zone of bone thickening.

The nidus may lie within the spongiosa, perhaps close to an articular surface, or may be associated with the cortex, and may lie against the inner surface of the cortex, within it, or even, though rarely, between the cortex and the periosteum.

The reactive perifocal zone is much more likely to be striking when the osteoid-osteoma is cortical than when it is within the spongiosa. In the latter case, one may find merely a zone of thickened, condensed, and otherwise altered spongiosa surrounding the nidus as a ring or band of variable extent. Thickening about a cortical nidus may extend over a considerable part of its circumference, especially when the lesion is in a long bone, which, furthermore, may be thickened for a number of inches longitudinally.

The nidus itself is usually roundish or oval, and is not more than 1 cm. in its greatest diameter. The clarity with which it shows up in the X-ray picture is affected by such variants as the position of the nidus in the affected bone; the radiodensity of the nidus itself; the extent and radiodensity of the perifocal zone of reaction; and the attention given to technique such as taking the picture from various angles, "coning down", overexposure, &c.

Against this general background, I shall now mention some cases illustrating various locations and various radiopathologic appearances of the osteoid-osteoma lesion.

FIG. 1.

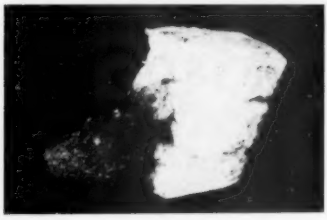

FIG. 2.

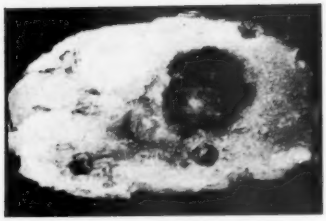

FIG. 4.

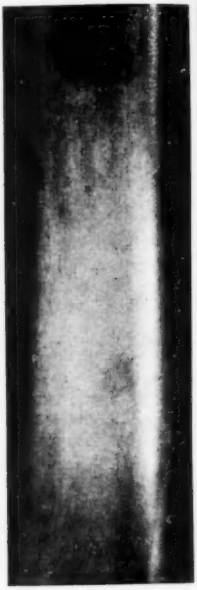

FIG. 3.

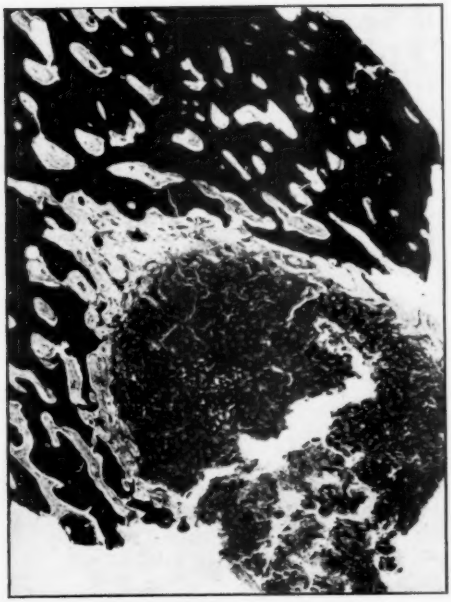

FIG. 5.

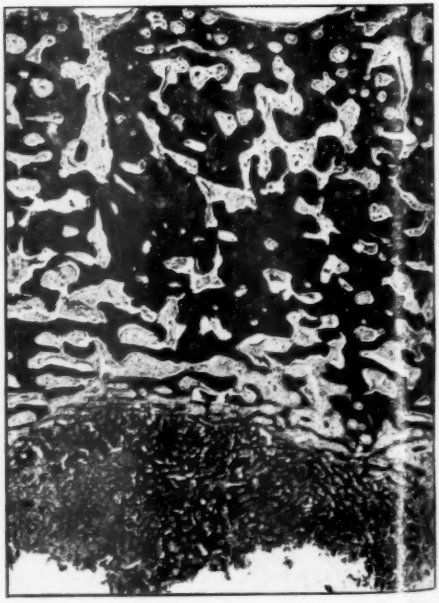

FIG. 6.

Case I.—A boy of 12 had suffered for one year from increasingly constant pain in the right hip and thigh. The lesion is slightly above the middle of the femoral shaft, and stands out clearly in thickened cortical bone (Fig. 1). When removed intact in its setting (Fig. 2), the nidus appeared as a dark red, gritty, friable tissue mass. The histologic pattern of the lesional area is shown in Fig. 5.

Case II.—A boy of 18 had complained, again for one year, of rather constant localized pain and some swelling in the lower part of the right leg. The lesion is in the lower third of the tibial shaft, and stands out fairly clearly as a roundish relatively radiolucent area in a setting of thickened cortex and spongiosa (Fig. 3). When removed intact in its setting (Fig. 4), the nidus appeared as a brownish globule of a friable but gritty tissue. The histologic pattern of the lesional area is shown in Fig. 6.

Case III.—A boy of 19 had suffered for two years from increasingly persistent and progressive pain in the right elbow region. In the X-ray film, the nidus stood out fairly clearly as a round focus of relative radiolucency set in an area of cortical thickening. When the nidus was removed intact in its setting, it was found to be a cherry red, granular, gritty tissue mass, 1 cm. in diameter.

This case illustrates that the nidus may fail to stand out against the surrounding thickened bone if insufficient kilovoltage is used in the exposure of the film. Indeed, radiographs taken under good medical auspices shortly before the patient came to us failed to reveal the nidus, and the observed thickening in the lower part of the humeral shaft was not ascribed to an osteoid-osteoma. However, when the lesion was coned down upon, and increased kilovoltage used in the radiography, the nidus came to stand out clearly, and all the data were harmonized for the correct diagnosis.

It should now be pointed out, however, that one also encounters cases in which, even under favourable radiographic conditions, a cortical nidus does not stand out as a clear-cut focus of increased radiolucency. When in the spongiosa at the articular end of a long bone, the nidus may present a relatively radiolucent or a relatively radiopaque shadow.

Case IV.—A woman of 49 had been suffering for two years from increasingly persistent pain in the left knee. An osteoid-osteoma was located in the spongiosa of the lateral condyle of the femur, at its lateral margin, just beneath the articular cartilage. The nidus appeared as a roundish, vaguely radiolucent area without evidence of perifocal reaction. Indeed, the presence of the nidus could be overlooked, as it was for a long time despite repeated X-ray examinations.

Case V.—In this case we are dealing with an osteoid-osteoma in the spongiosa at the upper end of a fibula. The patient was a boy of 19 who complained of pain of nine months' duration, localized to the outer aspect of the left leg, near the knee-joint. The nidus in this case contrasted with the one in the previous case, in that it stood out very well as a small, roundish radiopaque body, beyond which was a marginal crescent of densified spongiosa.

Case VI.—A boy of 16 had complained of pain in the right ankle for two years. The nidus, at the lower articular end of the tibia, appeared as a radiopaque body. The interesting question raised by this case was the differential diagnosis between osteoid-osteoma and osteochondritis dissecans. I have seen several instances in which an osteoid-osteoma presenting a radiopaque nidus at an articular end of a long bone was thought to represent osteochondritis dissecans until anatomic study of the removed tissue rectified that impression.

One or another tarsal bone (but especially the talus or the calcaneum) is not infrequently the site of an osteoid-osteoma. In relation to the calcaneum, the complaints are usually prolonged before the condition is recognized.

Case VII.—A medical student, 24 years of age, had suffered for sixteen months from progressive disabling pain in the right foot. Repeated X-ray examinations had been made but the findings had always been reported as negative, and the patient had consequently come to be regarded as a psychoneurotic. The X-ray picture taken a few days before surgical intervention showed the nidus located in the spongiosa toward the lateral surface of the calcaneum. It was small and round and not particularly conspicuous. It was surrounded by a rather narrow, irregular zone of radiopacity.

Case VIII.—A schoolteacher of 31 complained of pain in the right ankle, of three years' duration. During this time, she had had numerous radiographs taken of the ankle. The film that led to the surgical intervention shows an area of sclerosis in the calcaneum, beneath the subtalar joint, but the osteoid-osteoma nidus does not stand out particularly clearly within this general area of increased radiopacity (Fig. 10).

Only occasionally does one encounter an osteoid-osteoma in a carpal bone.

Case IX.—A man of 35 who complained of persistent, progressing pain in the right wrist, of one and a half years' standing. In addition, there was a point of exquisite tenderness over the semilunare, which showed a small, nidus-like focus of radiopacity. This case was particularly interesting because the radiopaque body seen in the X-ray picture represented an enostosis or "bone fleck" in which an osteoid-osteoma was developing.

Occasionally, an enostosis (which by itself is painless) is misinterpreted as an osteoid-osteoma because the patient is complaining of pain in the bone or joint area in which the enostosis is present. The example just given of an osteoid-osteoma developing *within* an enostosis is the only one we have encountered. It seems to represent one of those oddities which complicate but add to the interest of problems of clinical diagnosis.

A metacarpal or a metatarsal bone, or a phalanx of a hand or foot is likewise occasionally the site

of an osteoid-osteoma. In a phalanx, the nidus may show up as an area of radiolucency, or as a roundish core of radiopacity as in Fig. 8.

As to the involvement of bones of the trunk, an osteoid-osteoma in a vertebra is not uncommon. We have also seen one case with an involvement of an innominate bone (Fig. 11), and one of a rib where the lesion was in the posterior end of the right 11th rib (Fig. 9). The patient was a boy of 15 who complained of pain in the right flank and costovertebral region for about one year. Sneezing, coughing and hiccoughing aggravated the pain, and, in time, the patient developed a dorso-lumbar scoliosis.

The body of a vertebra is nearly always spared, the lesion usually developing in some part of the vertebral arch, or in a process. On account of the difficulty in obtaining good radiographs of these processes, the clinical diagnosis is often difficult.

FIG. 7.

FIG. 8.

FIG. 9.

FIG. 10.

FIG. 11.

Case X.—The patient was a boy of 15 with pain in the upper part of the back, and an area of spot tenderness over the 4th dorsal vertebra, on the left side. He eventually developed kyphoscoliosis. After fourteen months, the back was explored. An osteoid-osteoma was found which involved the pedicle and the adjacent part of the lamina of the 4th dorsal vertebra on the left side.

Case XI.—The patient was a girl of 10 who complained of progressive disabling pain in the back for almost a year. The lesion, in the upper aspect of the right lamina of the 2nd lumbar vertebra, shows in the radiograph as a roundish area of relative radiolucency, almost completely surrounded by a zone of relative radiopacity (Fig. 7). At surgical intervention, the nidus was found to be globular, red, partly soft and partly calcareous, and the size of a cherry.

Case XII.—In this patient, a young man of 21, there was a five-year history of back pain of increasing severity. The lesion was at the base of the left transverse process of the 2nd lumbar vertebra.

Some clinical considerations.—From these case presentations, one can gather that an osteoid-osteoma may develop in almost any bone, though we ourselves have not observed it in a skull bone. About 25% of our cases involved a femur, and about 25% a tibia.

The lesion seems to be at least twice as common in males as in females. Fully 75% of the patients are between 10 and 25 years of age. Few indeed are below 5 or over 50 years of age.

The duration of complaints at the time of admission for removal of the lesion is usually between six months and two years. Histories of less than six months are the exception, and only an occasional patient in our series gave a history as long as five years.

Probably the main reason for the delay in the clinical identification of the condition is that, during the early stages, it may be difficult to demonstrate the osteoid-osteoma nidus radiographically even under favourable technical conditions. Another reason undoubtedly is that the general medical practitioner—the one most likely to see the patient during the earlier part of the clinical course—is not likely to think of the possibility of an osteoid-osteoma.

The principal complaint is of pain, and it is this that consistently leads the patient to seek medical attention. Occasional and mild at first, the pain usually increases in persistence and severity, and often becomes bad enough to interfere with sleep. Fortunately, most patients learn quickly that an adequate dose of aspirin almost consistently relieves the pain for several hours at a stretch. The principal clinical finding is local tenderness—often exquisite "point" tenderness. I shall not attempt to discuss such clinical questions as the rather common finding of referred pain and the occasional finding of inexplicable neurologic manifestations. However, I would like to point out that, ordinarily, immobilization of the part does not relieve the pain.

Pathogenesis.—The evolutionary sequence in the development of the osteoid-osteoma lesion has always intrigued me (Jaffe, 1945), but I must forewarn you that I still do not feel that I understand it completely. The genesis of the lesion is, of course, the same whether in a spongy bone area or in relation to cortex. However, it is much easier to line up what seems to be a series of developmental stages for cortical lesions.

At a site where an osteoid-osteoma has started to evolve, the osseous tissue comes to stand out from the surrounding bone. The contrast is created by the effects of increased vascularization and active reconstruction at the site. In consequence of this, the original osseous tissue in the area comes to be resorbed and simultaneously replaced by new bone laid down in a process of creeping replacement. The new bone presents a rather atypical histologic pattern, and its deposition is most striking around blood vessels. Sooner or later, the overlying periosteum becomes stimulated to deposit new bone on the outer surface of the cortex.

Eventually, the area under reconstruction becomes completely converted into a nidus of closely compacted trabeculæ of highly atypical osseous tissue. Between these trabeculæ, there are numerous thin-walled blood channels set in a sparse stroma of osteogenic connective tissue. From comparative study of many lesions, one gathers that, if an osteoid-osteoma nidus presenting such a histologic pattern is not removed and thus has a chance to evolve further, the nidal area continues to undergo reconstruction. Its trabeculæ of highly atypical bone are reworked and resorbed, and a much more productive nidus comes into being. In the foreground of such a nidus, we now have a substratum of very vascular osteogenic connective tissue in which osteoid and osseous tissue in varying proportions are being laid down.

In fact, if one took an osteoid-osteoma nidus in this advanced stage of evolution out of its setting, it might quite reasonably be misinterpreted, in some cases, as a tumour field from an osteogenic sarcoma. The neoplastic aura is given it by the evidence of active osteogenesis within it. In fact, it is this aura of neoplasia that I had in mind when I gave the lesion the name of "osteoid-osteoma" in spite of its consistent smallness and apparently self-limited nature.

Treatment.—Surgical removal of the lesion is all that is needed to bring prompt and lasting relief. The nidus and some of the neighbouring bone may be removed with a curette, but this removal should be thorough, since otherwise there is danger of recurrence of the complaints. The only disadvantage

of curettement is a purely scientific one—namely that the tissue may be so crumbled that, unless the pathologist or surgeon is thoroughly familiar with the condition, he may fail to pick out the significant fragments (representing the nidus) for histologic examination, and thus fail to obtain confirmation of the clinical diagnosis. In acquiring experience with the lesion, I have sought, whenever possible, to obtain the nidus intact in its setting. This remains the procedure best calculated to facilitate wider understanding of the condition while abolishing the complaint of the patient.

What would be the ultimate state of our patients had there been no surgical intervention at all, we do not know. It is noteworthy, however, that, among them, a few had had complaints for as long as four or five years before the lesion was removed and relief ensued. Nevertheless, it is conceivable that an osteoid-osteoma might, after many years, undergo spontaneous clinical arrest or even anatomic involution: it will be difficult to collect evidence on this point, because of the severity of the clinical complaints and the usual ready accessibility of the lesion for removal. On the other hand, we do know that if, in the course of the operation, the osteoid-osteoma is not removed or destroyed, the clinical complaints are either not relieved at all, or, if relieved, recur after a variable time.

As to the effect of irradiation therapy on an osteoid-osteoma, little is known. One interesting case in point was that of a boy of 15 when a humeral lesion which had troubled him for a year was diagnosed as an osteoid-osteoma. At that time, he had received a course of ten X-ray treatments (of 200 r each) against the lesion. After temporary aggravation, the pain was relieved for almost three years. His complaints then recurred, and, after they had persisted for about a year, the lesion was excised. During the entire preceding five years, the osteoid-osteoma had remained visible radiographically. On histologic examination of the tissue removed at operation, an osteoid-osteoma nidus was still clearly identifiable.

Finally, I shall describe a case (the only one I have seen) of a recurrence at the site of the original lesion. In 1938 at the age of 3, a girl was treated for what was supposed to be a "sclerosing osteitis of Garré" affecting the left tibia. In the tissue then removed, an osteoid-osteoma was observed. Unfortunately, the original radiograph is not available. In 1952, at the age of 17, the patient was readmitted on account of complaints of one year's standing, again referable to the upper part of the left tibia. The tissue now removed showed again an osteoid-osteoma nidus. It is difficult to decide whether this second lesion represents a recrudescence of the first or the formation of a new one at the same site. The case merely calls attention to the possibility of what one may neutrally call a "recurrence" of an osteoid-osteoma, after a thirteen-year interval of freedom from complaints between the original and the second lesion.

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Section of Surgery

President—Professor F. A. R. STAMMERS, C.B.E., T.D., Ch.M., F.R.C.S.

[*May* 6, 1953]

DISCUSSION ON THE SURGICAL TREATMENT OF PAROTID TUMOURS

Dr. H. Redon: The parotid gland occupies a space bounded by muscles and fascia, and even with the most careful clinical examination the nature of a tumour, and even its origin, cannot always be recognized exactly. We must therefore consider all tumours of the parotid region as a class.

In the course of about fifteen years I or my assistants have operated up to date upon more than 350 tumours of this region. This large series is the basis of this paper.

Table I includes all the cases operated on up to January 1, 1953. Glandular tumours, true tumours and inflammatory lesions make up the great majority: 289 out of 326 cases.

TABLE I

Experience based on 326 cases of parotid tumour. Distribution of tumours operated on up to January 1, 1953

Mixed tumours	165	Unclassified tumours	37
Parotiditis	33	Nervous	6
Cancers	31	Vascular	6
Cystoadenolymphomas	18	Glandular affections	17
Other tumours	37	Connective tissue	8
Cylindromas	5		

From this list it is possible to establish the relative proportions of these tumours with some accuracy. Nearly half are mixed tumours, 47%. In France we call them epithelioma with modified stroma; 26% are primary or secondary cancer, nearly 10% parotiditis and 5% cystoadenolymphomata. Cystoadenolymphoma is more frequent than is supposed. These tumours have become well known only since about 1945, and a fairly large number of tonsillar cysts were probably confused with them before this. The very small number of cylindromata is due either to chance or to the interpretation of the pathologists. The unclassified tumours, as Table I shows, include 6 nerve tumours, 6 vascular tumours, 17 glandular affections, and 8 connective tissue tumours.

Nerve tumours, of which there are 6, are therefore not exceptionally rare. They must be considered for two reasons:

Firstly, some develop at the expense of the facial nerve, without any clinical sign to raise a suspicion of their presence and their discovery only at operation is a tragedy. The likelihood of a nerve tumour must be considered beforehand in order to be able to decide if the nerve is to be sacrificed. The question of possible involvement of the facial nerve should therefore always be discussed beforehand with the patient's family and physician.

Secondly, certain neurinomata or schwannomata are malignant tumours, requiring very extensive operation, and others may be a part of Recklinghausen's disease.

These facts show the need for histological examination during operation.

The vascular tumours are really congenital lesions: hæmangiomata, lymphangiomata or hæmolymphangiomata; they are regional, not glandular, lesions, and if surgical intervention is necessary, the operation is one of the most difficult to perform.

The glandular affections include various lesions, all related to lymphomatosis, which is the typical lesion of Mikulicz's disease.

The connective tissue tumours comprise non-glandular cysts, one histiocytoxanthoma and one lipoma.

This region is therefore the site of very varied tumours. With rare exceptions, a definite differential diagnosis for all these tumours is impossible pre-operatively.

New methods of diagnosis.—I have carried out nearly fifty sialographies, of which not one has corrected a clinical diagnosis, and some have given false information. On the other hand, radiography can be useful, not often in glandular lithiasis, which is difficult to see, but definitely in calculi of Stensen's duct provided an intrabuccal film is used for X-ray of the region.

Cytological examination of the saliva is of no help. An ulcerated carcinoma in the excretory ducts is easy to diagnose, and cytological examination is of no use for other tumours. Drilling puncture should give valuable information.

Biopsy in parotid tumours.—Biopsy is indefensible because of the danger to the facial nerve. No clinical diagnosis can make absolutely sure of the position of the parotid tumour in relation to the nerve. Any removal of tissue entails the risk of cutting the nerve or one of its branches. The nerve must therefore be found before a fragment of the tumour is removed; in other words a deliberate operation, i.e. not merely a biopsy but a first stage of a parotidectomy must be performed. This is the only way of putting into effect the treatment indicated for these various tumours.

It is therefore necessary to find the facial nerve where it emerges from the stylomastoid foramen and to trace it as far as its bifurcation. It is then generally possible to see if the tumour is in the superficial or in the deep lobe of the parotid. The nerve spreads in the plane of cleavage between the two lobes. If the tumour is superficial it can be removed forthwith. If the tumour is deep it may have to be dissected out and the biopsy can then be safely made. The specimen should be examined at once and the operation can then be completed. If histological examination during operation is not possible, the tumour should be removed, but its histology should be determined as a matter of urgency. The skin wound is closed, and the operation can be completed in a day or two.

This procedure, of course, is applicable only to circumscribed non-malignant tumours.

When a probably malignant tumour is encountered, it is necessary to take the responsibility of carrying out a mutilating operation at once, with section of the facial nerve, or of sending the patient to a surgical centre where histological examination of a biopsy can be carried out during operation.

Treatment of tumours of the parotid region.—I shall refer only briefly to the tumours whose treatment is generally accepted and I shall deal more fully with the so-called "mixed" tumours, i.e. epithelioma with modified stroma.

(1) *Malignant tumours*: These may be tumours of the gland or intraparotid glandular metastases. The glandular tumours themselves may be primarily carcinomatous or altered epitheliomata with malignant changes. The latter are by far the less malignant. If the tumour is intraglandular, these cancers demand total parotidectomy *en bloc*, without dissection of the facial nerve. If the tumour has spread beyond the gland an "extended" parotidectomy must be carried out, with a more or less extensive sacrifice of skin, of the mastoid, and of the sterno-cleido-mastoid muscle, of the masseter or the ascending ramus of the mandible, of the pinna and of the stylomastoid foramen. The parotidectomy must be completed by removal of the cervical lymphatics. Complementary treatment with X-rays is usually given, although these tumours show little or no radiosensitivity. The prognosis is, on the whole, very bad, and not more than 10% of cases survive for five years.

Intraglandular metastases—I refer only to the primary metastases of healed or unrecognized cancer—need the same operation. The possibility of a nævocarcinoma must not be forgotten, as in this type of tumour, which is not uncommon, massive electrocoagulation of the whole area is absolutely necessary.

Inoperable tumours.—The chemo-surgical method revived by Mohs, i.e. the local application of a caustic paste, gives some unexpected cures.

Cylindromata and mixed tumours with active malignant growth.—The cylindromata are characterized by a tendency to form pulmonary metastases. They are also highly radio-sensitive (Baclesse). In these cases total parotidectomy must be supplemented by intense radiotherapy in order to avoid recurrences.

Degenerated mixed tumours.—Preservation of the facial nerve is only possible if the tumour is clear of the nerve and can be removed *in toto* together with the gland.

(2) *Chronic inflammatory lesions* (tuberculous parotiditis, calculous or non-calculous recurrent parotiditis, lymphomatosis, hæmolymphangiomata) require total parotidectomy with preservation of the facial nerve.

(3) *Benign encapsulated tumours* (lipomata, cystoadenolymphomata, benign schwannomata and cysts) should be treated by simple enucleation.

Intraparotid papillary cystoadenolymphoma is a benign tumour which occurs mainly in men 50–70 years old (76% of cases). It forms 2% of all tumours of the head and neck, 5–6% of all parotid tumours, and 10% of all benign tumours of the gland. We know of at least 102 published cases. Since November 7, 1946, Professor Delarue has seen 27 cases. They are seldom diagnosed, except at operation, and either adenitis or Leroux's epithelioma with an altered stroma is usually

suspected. Generally the diagnosis is only made by the laboratory. Here the juxtaposition of lymphoid and epithelial tissues is recognized, with the characteristic structure of the papillary cystoadenoma described in Albarran's original case (1895). Rejecting the many dysembryoplastic hypotheses held abroad, Menetrier (1923) and Letulle (1927) already supported the histogenetic theory.

Dilatation of an excretory duct occurs as a result of an unknown inflammatory or non-inflammatory cause. Intracystic villous hyperplasia of the stratified cylindrical lining of the duct follows, with proliferation of the lymphoid tissue, which may or may not be organized into closed follicles, as is usual in all subacute chronic inflammations of the salivary glands. There is no question here of lymphatic heterotopia.

That this is a non-congenital, benign neoplasm is confirmed by the following facts: The recent discovery that these changes begin in modified glandular lobules, infiltrated by lymphoid elements, i.e. pseudo-glandular. The presence within the tumour of parotid acini. The structure of the micro-cysts, whose appearance is so like that of rudimentary salivary ducts. The existence of cystic excretory ducts, already surrounded by lymphoid tissue, within the normal gland and at a distance from the new growth. The possible occurrence of identical findings in simple chronic parotiditis. The impossibility of explaining the papillary cystoadenolymphoma of the submaxillary gland by the branchial developmental theory (Wendel and Spitenagel). Enucleation of these tumours always results in a permanent cure.

(4) *So-called "mixed" tumours*: These tumours are epithelial tumours, i.e. modified stroma epitheliomata. Cellular metaplasia explains the many tissues which may be found in them, and an intense connective tissue reaction seems capable of explaining their slow evolution, low-grade and mainly local malignancy.

These tumours have been found in all the salivary glands, in the bronchi, in the anal canal and in the fingers. The so-called "mixed" tumours are remarkable for their rapid recurrence; three, four or five recurrences are not infrequent, the rates varying from 16 to 40%.

There comes a time in the development of these tumours when they behave like true malignant tumours, complicated by pain, facial paralysis and ulceration. This malignant development may be very rapid. Naturally these recurrences are difficult to operate on.

Classical enucleation has therefore been abandoned, being, rightly, accused of promoting recurrences, for it has long been known that these tumours have only a false capsule. It has therefore been suggested that enucleation should be replaced by enucleation-resection or resection. This type of operation has, however, never been carried out. This is easy to understand, because, the principle of this operation being extensive resection of the segment of the parotid containing the tumour, cutting of the facial nerve is both likely and inevitable, and surgeons have always preferred the risk of a possible recurrence to the certainty of immediate facial paralysis.

In 1908 Pierre Duval suggested total parotidectomy with section of the lower branch of the facial nerve and preservation of the palpebral branch. This operation was not acceptable, because of facial paralysis, and surgeons continued to perform enucleations and mixed tumours continued to recur.

In 1934 I first performed a total parotidectomy with complete preservation of the facial nerve, and since then I have always done this operation, except in cases of clinically recognized cancer. With the technique used, it is possible to cure inflammatory lesions of the parotid without deformity, and, above all, a permanent cure of the so-called mixed tumours is ensured.

This operation has also enabled the entire glands to be examined histologically, and Professor Jacques Delarue has drawn conclusions from such examinations which make it necessary to alter the classical treatment, and which condemn out of hand both resection and enucleation.

In 1941, while studying a specimen obtained by parotidectomy from a patient with a third recurrence, Delarue was surprised to find, in addition to the clinically recognized tumour, eight isolated, independent nodules of mixed tumour. He thought at first that they were simply inoculations, but he later found "aberrant foci" not only in cases of recurrence, but also with primary tumours.

The incidence of tumours with multiple foci varies from 20 to 33%. In other words, one enucleation out of three or five will be followed by the development of one or more further tumours. Sometimes there is only one aberrant focus, but there are often several, and in one case Professor Delarue found 21. They may be near the principal focus—which is the rule—or at some distance, and they may be either in the diseased lobe or in the healthy tissue.

The problem of recurrences must therefore be considered again. A study of them shows that they occur in two conditions. Some occur early in the scar itself or in its immediate neighbourhood. These are really seeded tumours. The fact that the false capsule has often been broken through by the surgeon explains these events perfectly; no technique of enucleation can avoid them. The others occur late, even very late (five, ten, fifteen years later); they are often far from the scar and correspond with the growth of one of the aberrant foci; no method of resection can avoid them. Both types may appear together, and there are not infrequently several foci of recurrence.

I have never yet observed any recurrence of mixed tumours treated from the first by extensive resection, i.e. by total parotidectomy. On the other hand, there have been three recurrences after parotidectomy for recurrent tumours. In these three cases, however, the recurrences took place in the scar of the first operation, and I am sure that they represent the growth of remnants of tumour

left behind at the first operation. I think, therefore, that in repeated operations, total parotidectomy must be supplemented by wide resection of the scars of previous operations. The scar must be surrounded by the incisions and removed with the gland.

One point of paramount importance must be emphasized. Early recurrences, though they may be histologically identical with the first tumour, differ from it by one constant characteristic. The tumour is now not encapsulated but diffuse, and shows all the local characteristics of a malignant tumour. Any economical, limited operation is necessarily followed by a further recurrence. If we add that the region has been altered by the tumour, by the operation, by cicatrization and by the development of the false recurrence, it becomes obvious that parotidectomy with isolation of the facial nerve is the only possible operation if we wish to avoid paralysis as well as to cure the patient.

My conclusions agree with those of Mr. Bailey. Large glands are often found touching the lower pole of the parotid. These are in most cases inflammatory, but in one case a gland of this kind contained a true metastatic epithelioma, the parotid tumour being a mixed tumour, and in another case a true cancer of the parotid coexisted with a nodule of epithelioma with modified stroma in the gland. These facts show that biopsies must always be made.

During operation the facial nerve may be cut, either by accident or from necessity; it has happened in my own experience six times, and I have been able to confirm that accurate suture is always followed by complete restoration, provided there is no displacement of the ends of the nerve. If the nerve is sacrificed, grafting gives almost invariably good results. I have successfully used the ascending branch of the superficial cervical plexus, which is always traced and cut at the beginning of the operation, and have found it perfect. Finally, if grafting and suture are both impossible, it is advisable to resect the superior cervical sympathetic ganglion during the same operation. This palliative procedure, recommended by Professor Leriche, seems to be of little use in old facial paralysis, but it gives considerable relief to the ocular discomfort if it is carried out as early as this.

Conclusion.—Total parotidectomy, though it produces only very slight disfigurement, is fairly often complicated by a syndrome described long ago by Frey in certain sequels of otitis. This consists of an abundant flow of sweat in the parotid region during meals. This temporary flow is often accompanied by congestive redness of the same region. This syndrome, whose origin is still a mystery, sometimes does not appear until months after the operation, and may or may not disappear later. Finally I have never seen any salivary fistula after my cases in a fairly large number of subtotal parotidectomies carried out for benign tumours, other than mixed tumours.

(A film of total parotidectomy was then shown. Slides were also shown throughout the address.)

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Mr. G. M. Fitzgibbon (Bristol): Many writers have stressed the high recurrence rate, which even to-day is one of the outstanding features of the after-result of the surgery of parotid tumours. There are a number of reasons for the high recurrence rate; and one very obvious one is the tempting nature of the average parotid tumour. Most of the typical so-called "mixed" tumours, for some reason which has not been explained, are situated in the lower half of the gland. They are so mobile and appear to be so obviously encapsulated, and frequently superficial, that they almost ask to be "shelled" out. They create a completely false impression of the real difficulties which may be encountered, and one danger is the fact that the capsule may be incomplete in places and in some cases invaded (Fig. 1).

Parotid tumours are often larger when excised than they appeared to be on clinical examination beforehand and frequently situated more deeply than was apparent. I regret to say that enucleation of these tumours is still advocated by some teachers, and probably most of us know and have experienced the difficulties of this procedure—a small inadequate exposure, pools of blood, no real sight of what is being done, bursting or breaking of the tumour with contamination of the wound.

I have on two occasions seen small satellite tumours closely associated with the main one, and I have seen these referred to by other writers. Here then, is another possible cause of recurrence. An interesting observation made by McFarland (1936) is that recurrence more commonly follows the removal of small tumours. He suggests as a remedy that they should be allowed to grow to a larger size before removal. Professor Willis (1948) puts forward what seems to me the real answer to this observation by suggesting that a zone of salivary tissue is potentially neoplastic and these tumours may well be multicentric in origin. This, perhaps, is confirmed by the occasional report of satellite tumours, and an excision of the whole area is obviously the correct answer and is the justification for the removal of an area of apparently normal gland around the main tumour.

I am sure also that much of the confusion that exists in surgical practice to-day, is partly due to the misleading names which have been used in the past to describe these tumours. An essential

fact to be remembered is that the vast majority of parotid tumours are epithelial in origin and exhibit a wide range of structure and behaviour. They form a large group of tumours which merge almost indistinguishably from simple adenomata to frankly malignant adenocarcinomata. It is true, also, to add that the histology of any given tumour is not always a guide to the prognosis.

A long and involved argument went on for many years over the question as to whether these tumours contained cartilage or not, and other points of histological importance. I am sure that the obscure and ill-defined teaching about the histology is another reason for the failure of many surgeons to appreciate the real problem. There are two objectives in treatment. (1) To cure the patient of his disease permanently. (2) To do so without serious disfigurement or deformity, if possible.

In the past, these objectives have too often been placed in the reverse degree of priority, and fear of the facial nerve and/or the development of a fistula has dominated the situation and clouded judgment on the matter.

These tumours grow very slowly, and may be present for many years before any action is taken either by the patient or by his doctor. It has been stated that many of them never become malignant, but it is probable that this is not true, and in any case it does not constitute a valid reason for leaving them alone. For one thing it is not possible to know which will become malignant, nor is it possible to forecast which of them will reach a large size, and need to be removed for cosmetic reasons.

And finally it is, I think, stretching a definition too far to refer to them as benign when many of them are not completely encapsulated, sometimes infiltrate locally, show a recurrence rate of 20% to 25% and even occasionally produce metastases.

Many writers refer to the results of treatment by varying forms of irradiation. The reports have

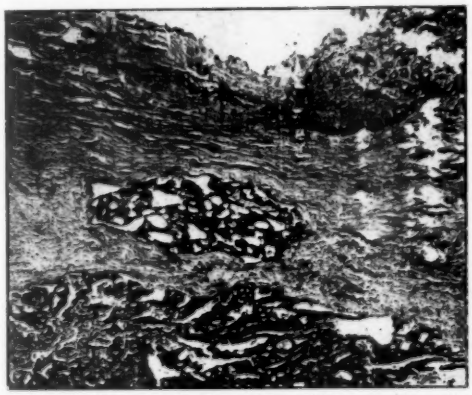

FIG. 1.—Section showing an island of tumour in the centre of the capsule wall which could very easily be left behind in the process of enucleation, thus leading to recurrence. × 40.

been uniformly unfavourable. Janes (1943) reported, after a long study of a large number of cases treated by different radiotherapists at several centres, that he knew of no good being done, and observed some deep penetrating radionecrotic ulcers associated with severe pain. Personally, I have seen no good come from irradiation and I believe that the following-up of a surgical excision by irradiation is not only bad practice, but is surely an admission that the operation has been, or may have been, inadequate. Figs. 2 and 3 are examples of unsatisfactory irradiation treatment.

Parotid tumours are not very common. Over the last five years, I have knowledge of some 42 cases. I was concerned in the treatment of 19 of them and the other 23 were treated by different surgeons. The youngest of the 42 cases was aged 14 years and the oldest was 87 years and there was a slight preponderance of females, 23 to 19 males. Of the 19 cases I was personally connected with, 4 were carcinomatous and I deliberately sacrificed the facial nerve in 3 of them. I was able to preserve the nerve of the fourth case. So far there have been no recurrences among the 15 known non-carcinomatous cases, but this is not significant as recurrence is slow and the average time for recurrence to take place is seven years or longer.

I have given up any form of local removal or enucleation because I believe it to be completely unjustified. I was interested to see that among the 23 cases treated by other surgeons, the operation performed on 5 of them was described as enucleation. Of these 5, 2 were reported histologically to be adenocarcinoma although it was not suspected clinically beforehand.

The cure rate of parotid tumours should be far higher than it is. I regard an adequate removal as a difficult and time-consuming operation. I prefer to operate with the patient tilted on a steep slope, with the head high, and, in suitable cases, prefer to employ a hypotensive form of anæsthesia.

A really adequate incision with complete exposure of the whole gland is important, and need not be at all unsightly afterwards if well placed and nicely sutured.

I always use an electric stimulator attached to my dissecting forceps, which was constructed by my colleague, Mr. D. C. Bodenham (1948). In simple language it causes a small faradic current to flow through the forceps. The current is so small that no movement of the face results unless the jaws of the forceps are within 2 or 3 mm. of a branch of the nerve.

I try to identify the cervical branch first and work upwards towards the main trunk.

FIG. 2.—Two years earlier this girl had a small tumour removed from her right parotid by enucleation, followed by the insertion of radium needles. The recurrence (shown in picture) was adenocarcinoma and in spite of an extensive excision of the whole gland and the glands of the neck, she died two years later from multiple blood-borne metastases.

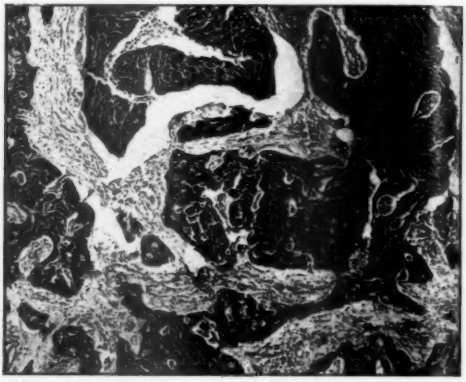

FIG. 3.—Section of a parotid tumour heavily irradiated six years previously without any noticeable difference in size, showing extensive malignant areas. The epithelial cells are markedly squamoid in appearance and the tumour is of an anaplastic type with numerous mitoses. × 40.

Then one comes to the much debated isthmus, which I think is a poor thing and ill-defined, but there is no doubt that the main communication between the superficial and deep parts of the gland lies between the two primary divisions of the facial trunk. Having found the main trunk and divided the somewhat vague isthmus, I work forwards, free each branch of the nerve, and preserve it if possible. I have been interested to notice how frequently one can divide small branches without any obvious weakness of the face afterwards. I have also been amazed at the way in which one can cut across the gland without ever being bothered by a persistent salivary fistula afterwards; I usually put a small drain just below the ear for forty-eight hours. Familiarity with a technique of this type enables one to remove large tumours with little or no permanent disfigurement.

(Several cases were described at this point, illustrating the different types of tumours which may be encountered.)

To sum up, therefore, parotid tumours are, in the main, epithelial in origin and should be described (Willis, 1948) as pleomorphic adenomata and adenocarcinomata and that there is no real distinction between any of them. The real difference is one of malignancy only. The terms "simple" and "mixed" should be abandoned. They are misleading and inaccurate. There is nothing which could be said to be "simple" about the histology or treatment of these cases and the tumours are now known not to be "mixed". As regards treatment, adequate and extensive removal of the whole area, taking a large part of apparently normal gland around the tumour away as well, will give the best results with the fewest possible number of recurrences.

And lastly, I believe there is no place at all for the use of irradiation in the treatment of these tumours either pre- or post-operatively.

I should like to acknowledge with thanks the courtesy of my colleague, Mr. D. C. Bodenham, for permitting me to use the slides of some of his cases and for the preparation and construction of the film. (An illustrative film was then shown.)

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Mr. D. N. Matthews: *Repair of facial palsy.*—No operation has yet been designed which simulates the normal play of facial expression either accurately or completely. It is, therefore, of great importance to take every possible precaution to avoid damaging the nerve. The nerve detector, designed by Bodenham, is extremely useful in this connexion. I find that by connecting the electrode to the knife or scissors one gets ample warning when approaching a branch of the nerve. The face starts to twitch when the point of the instrument is about a millimetre from it.

It is essential to repair the soft tissues if they have been damaged, before contemplating disguise of the palsy itself. If the skin has been damaged either by irradiation or by surgical excision the loss can conveniently be made good with a large rotation flap which is either brought down from the scalp or up from the neck. In the rare event of the loss involving the full thickness of the cheek with a fistula into the mouth, the repair must reconstitute the mucosal lining as well as the skin cover. There are several ways of achieving this. Small fistulæ can be closed by turning skin flaps, based on the margins of the defect, inwards to restore the lining, and by providing a separate pedicle flap for the cover. For larger defects the lining is best provided by a free skin graft placed on the under side of a pedicle flap from the chest. If this method is chosen the appropriate part of the pedicle is lined with the skin graft before it is brought up to the face. I prefer this method in most cases since it produces a repair which is of the right thickness and of reliable vascularity.

Indications for treatment of facial palsy.—Of the many indications for treatment, danger or damage to the eye is perhaps the most urgent. Severe conjunctivitis often occurs together with troublesome epiphora. These conditions must be attended to rapidly if severe complications are to be avoided. Drooling of saliva from the paralysed angle of the mouth and the collection of food in the buccal sulcus also require attention, as does the cosmetic disability which frequently makes the patient so self-conscious that life is intolerable. If the palsy has resulted from the excision of a malignant growth, however, the advisability of further interference must be carefully weighed. In my opinion no reconstructive operation should be performed which involves interference with tissues close to the site of the primary tumour until there is reasonable certainty that it has been completely eradicated. In some instances it will be necessary to postpone facial reconstruction for many months on this account.

When to operate.—When presented with a case of facial palsy it is sometimes possible to decide with fair confidence whether the nerve has been divided from a study of the case history and the operation notes. For example, the nerve may have been carefully identified, with or without a nerve detector, and considerable care taken to avoid injuring it; or the tumour may have been small and encapsulated. Under such circumstances it is, I believe, desirable to wait as long as a year, even in the presence of a reaction of degeneration, and with no clinical sign of movement on the affected side. This is because it is impossible to avoid some damage to the facial muscles however carefully the reconstructive operation is performed, and this may just be sufficient to prevent the ultimate achievement of a degree of recovery which is cosmetically acceptable. Operation should always be postponed in a recovering lesion so long as recovery continues.

If an electromyograph and an experienced interpreter of its results are available it is sometimes possible to decide sooner if an operation is needed. This instrument is, however, of practically no value without an experienced interpreter of the sounds which it emits. Such an expert will be able to deduce the likelihood of recovery from the strength of the sounds produced, their duration, frequency, periodicity and character. In the absence of evidence of recovery with this instrument after six months the chances of much, or indeed any, recovery are slender. If the noises of fibrillary twitching are heard, indicating muscular degeneration, no recovery can be expected, and operation can then be carried out forthwith.

Treatment whilst awaiting operation.—(*a*) *Physiotherapy:* Whilst awaiting recovery it is necessary to treat the patient daily with galvanic stimulation in order to preserve the contractability of the muscles. In a recovering lesion active facial exercises should be encouraged. These consist of grimacing in front of a mirror in such a way as to exercise all the main muscle masses. Faradism plays no part in the treatment of a recovering lesion except perhaps to teach a child how to grimace as is required. The use of faradism over long periods of time leads to an ugly hypertrophy of the affected muscles which makes the appearance worse.

(*b*) *Suspension:* It is essential to preserve the paralysed muscles from passive over-stretching whilst awaiting their recovery. The best procedure is to fix a prosthesis in the angle of the mouth by attaching it to a cap splint on the upper teeth. It can conveniently be made of flesh-tinted acrylic resin, when its presence is scarcely discernible. A cap splint cannot, however, be fitted to the milk teeth and this method is, therefore, inapplicable to cases of paralysis in young children. It is also inapplicable to the edentulous. Under such circumstances a hook should be fitted to the angle of the mouth and held by suspension with one side-piece of a spectacle frame carried over the ear. It is desirable to fix the hook to the spectacle frame with an elastic band since rigid fixation is attended by a risk of ulceration at the corner of the mouth.

Suspension may also be achieved with strips of adhesive plaster. These are attached to the lower eyelid, cheek and lips and pull in an upward direction being fixed to a piece of elastic fastened over the top of the head. This is a clumsy method of suspension but has the merit of simplicity.

(c) *Care of the eye:* The eye needs constant attention whilst the patient is awaiting operation. An eye-shade must be worn when the patient is exposed to bright, hot sunlight or to a dusty atmosphere. A dark glass with a side cover is satisfactory. The cornea must also be protected from drying by the instillation of Paroleine drops. This is particularly important during the night in hot weather when the globe is inevitably exposed for several hours. If conjunctivitis supervenes appropriate local chemotherapy must be instigated at once, whilst if it recurs lateral tarsorrhaphy may be necessary.

Operation.—The symmetry of the mouth is restored by a static fascial sling which encircles the mouth and is interlocked with a second sling attached to the temporal fascia after the method described by Kilner. Reanimation of the face is attempted by use of the muscles of mastication. A strip from the centre of the temporalis muscle is made to reach the eyelids and a piece of the masseter muscle is turned forwards to the angle of the mouth. The temporalis muscle is approached through an incision, similar to that used for cosmetic face lifting, and the surplus slack skin is excised when the wound is closed. The masseter is approached through a separate small incision beneath the body of the mandible. The droop of the lower eyelid is corrected by attaching its outer end to the upper lid, thus making use of the unparalysed levator muscle (lateral tarsorrhaphy). The punctum of the lower lid is turned inwards to gain apposition to the globe by means of a modified Z-plasty at the inner canthus. At first the patient has to clench the teeth as a deliberate act in order to achieve a smile, and must practise before a mirror to learn how much contraction is needed. Dissociated movement without the necessity for conscious effort may not be attained for many months in an adult. It usually takes less time in a child.

Finally, it may sometimes be desirable to fit an upper denture with a projection into the buccal sulcus to fill out the cheek if muscle wasting has produced considerable hollowing. (A film illustrating the results of these procedures in 3 patients was then shown.)

Mr. David H. Patey first paid tribute to Dr. Redon's authoritative contribution, and mentioned the names of two British surgeons who were also pioneers in the establishment of the idea that total parotidectomy with preservation of the facial nerve was a feasible surgical procedure—Mr. Hamilton Bailey of London and Professor Janes of Toronto. Parotidectomy was providing a new order of pathological evidence, in that the relation of the tumour to the surrounding gland could now be accurately studied. He mentioned 9 personal cases in which such intensive studies by serial section were being carried out at the Middlesex Hospital by Dr. A. C. Thackray. He showed slides demonstrating that mushroom-like nodules and infiltrating columns of cells were common in the normal parotid gland around the main tumour, but stated that so far serial sections had always shown that such nodules and columns were confined to the glandular tissue in the immediate neighbourhood of the main tumour with which they were directly connected, and that evidence of multicentric tumour nodules had not been found. Excision of the tumour with a zone of normal glandular tissue around it on all sides, after the facial nerve and its branches had been first dissected out, would on this evidence be a sound operation pathologically, but in practice in most cases this would mean a superficial or a total parotidectomy. On this basis, early operation while the tumour was still small would be an advantage, since at this stage there would be a greater likelihood of removing a margin around the tumour without total parotidectomy. If studies should, however, show that multicentric nodules were at all common, then routine total parotidectomy would be indicated. He concluded that with the establishment of a sound technique of parotidectomy with preservation of the facial nerve, such as Dr. Redon had demonstrated, there was good reason for abandoning the operation, pathologically unsound, of enucleation.

Section of Proctology

President—O. V. LLOYD-DAVIES, M.S., F.R.C.S.

[*May* 13, 1953]

DISCUSSION ON THE SURGERY OF ULCERATIVE COLITIS

Dr. Richard B. Cattell (Department of Surgery, The Lahey Clinic, Boston, Massachusetts): The management of patients with ulcerative colitis is a difficult clinical problem. To obtain the best results it is almost essential to have a team of physicians comprising an internist or gastro-enterologist and a surgeon. When these patients are seen and followed by physicians interested in both their medical and surgical care, surgery is less likely to be delayed when complications occur and, on the other hand, the internist or gastro-enterologist will provide a proper conservative approach as well as carry the responsibility for continued treatment. For a period of twenty-five years at the Lahey Clinic, this type of combined management of patients with ulcerative colitis has been carried out and proved of great value. This is not only possible but almost a necessity when large numbers of patients with this disease are encountered and their management constitutes a daily problem. It is my purpose in this discussion to present the experiences of our surgical staff in the management of ulcerative colitis.

Ulcerative colitis is a non-specific inflammatory disease beginning in the mucosa of the colon and progressing by direct extension through all coats of the bowel and in continuity both proximally and distally. It usually begins in the distal colon or rectum and rarely may remain localized or segmental but usually progresses to involve all of the colon in varying time intervals and in over 10% of cases comes to involve the distal small bowel. It may be manifested by one or more acute attacks which usually progress to an intermittent or continuous chronic phase. The progression of the involvement in continuity is an important observation in planning surgical treatment.

The ætiology of ulcerative colitis is unknown. It is most frequently observed in the temperate zone, and rarely observed in the tropics or warmer zones. No specific organism has been proved to be the cause although several have been implicated. Among the factors which play a part in its origin or progression are food sensitivities and allergic manifestations, spasm of the muscle coats, pre-existing infection such as amœbic or bacillary dysentery, thrombo-embolic phenomena, psychosomatic or psychiatric disorders and possible abnormal function of the sympathetic nervous system. There is much to suggest that it is an environmental disease not unlike exophthalmic goitre or peptic ulcer.

Since this disease must be treated without knowing its cause it is treated empirically as an infection with an attempt to eliminate any of the above-mentioned factors. An acceptable explanation as to the origin of ulcerative colitis may be stated as follows: When a break in the integrity of the mucosa of the large intestine occurs or the mucosa becomes permeable from any cause, a non-specific infection may occur. If the natural resistance of the patient aided by supportive medical measures does not enable us to arrest this infection it may become progressive and develop into ulcerative colitis.

All patients with ulcerative colitis should be treated medically and by this means the disease may be arrested, though not cured, even though complete remission can be produced with no demonstrable traces of the disease left. Such a patient is always susceptible to recurrence and it usually accompanies some intercurrent infection. Symptoms are intermittent and there may be long periods of remission, so that the success of treatment can be evaluated only after a long follow-up period.

The number of patients who are considered failures of medical treatment is dependent upon the extent, severity and duration of the disease. In our earlier experience (Cattell, 1948; Cattell and Sachs, 1948) only 25% were considered to require surgery. However, as one follows these cases for longer periods of time the number who have complications that require surgical treatment constantly increases so that at the present time in our experience approximately one-half are submitted to operation.

After operation the surgeon should accept the responsibility not only for their immediate care but for an indefinite period that may be the lifetime of both the patient and the surgeon. The problem of the proper management of an ileostomy may be a complex one and more or less continuous guidance is needed. Fortunately, the patient with proper instruction from the surgeon becomes quite expert in the care of his condition and seeks advice readily if anything untoward occurs.

It is important to discuss the operative procedures proposed with the patients and their families and the full confidence of the patient should be maintained. The patient becomes, quite properly, dependent on the surgeon who must be a practical psychiatrist.

Surgery provides complete rest of the infected bowel beyond the point selected for an ileostomy, and furthermore, by removing the infected bowel it provides the only certain method of cure.

Indications for surgery.—Patients who do not respond to medical treatment become candidates for operation. The indications are not unlike those for peptic ulceration of the stomach and duodenum. They may be listed as follows: (1) acute fulminating colitis; (2) hæmorrhage; (3) perforation and fistulas; (4) infectious arthritis; (5) obstruction; (6) malignant degeneration, and (7) intractability.

The patient who has acute colitis as manifested by high fever, prostration, weakness and bloody diarrhœa deserves a short period of active medical therapy but must be seen by both medical and surgical consultants. If the clinical course is not one of improvement within a period of four to seven days, ileostomy should be advised. It is in this group that the highest medical and surgical mortality occurs. The fact that some patients respond promptly to medical management with the use of blood transfusions, antibiotics, ACTH, complete rest and other supportive measures, has too often led to delay in advising operation when satisfactory improvement has not occurred. It is this delay and its fatal consequences that have been responsible for the high mortality following ileostomy and also for the reluctance of internists to recommend ileostomy. Too often free perforation into the general peritoneal cavity occurs and recovery is rare in spite of any form of treatment. We recommend early ileostomy in the first or second attack of acute colitis and under these circumstances the continuity of the ileum occasionally can be restored if ileostomy is followed by satisfactory healing of the colon. A lower overall mortality of ileostomy will result if early ileostomy is accepted in acute colitis.

Massive hæmorrhage in ulcerative colitis is rare, while chronic blood loss is almost the rule. If alarming bleeding continues after ileostomy, it is sometimes necessary to do colectomy within a few days of the previous procedure. Chronic blood loss resulting in severe secondary anæmia requiring repeated transfusions is a more common indication for surgery.

Subacute and chronic perforation of the large bowel is not frequent in the colon but is common in the rectal segment, resulting in fistulas to the bladder, vagina, perineum and ischiorectal fossa. It is a common cause of perirectal abscess. Local operative procedures in the perineal or perianal region, except for abscess, are contra-indicated. In all of these cases resection of the bowel is essential for cure. Occasionally, intra-abdominal abscesses in the region of the cæcum or sigmoid occur but they do not usually result in fistulous communications with the small bowel.

Infectious arthritis may be a troublesome complication in the medical management of ulcerative colitis. When other clinical manifestations of the disease are under control there may still be a progressing soft tissue joint change, and if it is permitted to progress, permanent joint deformity and loss of function may result. Under such circumstances removal of the colon is required and if done sufficiently early, satisfactory recovery of joint function should result. We have observed a number of patients who have refused surgical treatment and have become completely incapacitated and bedridden because of long-standing ulcerative colitis.

Varying degrees of obstruction may develop in the late stages of ulcerative colitis and may be present without remaining activity of the disease. Partial obstruction from gradual diminution of the lumen of the bowel is common. Localized obstructions in the colon occur following ileostomy and in a number of instances we have seen complete loss of the lumen demonstrated in the resected specimens.

The incidence of malignant degeneration in ulcerative colitis has been well recognized in recent years. Previous to the reports by Bargen and his associates from the Mayo Clinic (Bargen, 1928; Bargen and Dixon, 1935; Bargen and Sauer, 1944; Sauer and Bargen, 1949), only rare cases of malignant degeneration had been reported. While the overall incidence of carcinoma arising from ulcerative colitis is probably under 3%, if one considers the patients submitted to operation it rises to 5 to 12%. In our experience (Cattell and Boehme, 1946) with operated cases in which the patients had had the disease for nine years or more, the incidence was 33%. Lyons and Garlock (1951) found that of those followed for twelve years or more, carcinoma developed in 36%. The experience at St. Mark's Hospital as reported by Counsell and Dukes (1952) of an incidence of 11·1% in 63 operated cases more nearly parallels our experience. There is sufficient evidence available concerning the incidence of malignancy in long-standing ulcerative colitis to make it imperative to advise total colectomy in all patients with permanent ileostomy.

By far the greater number of patients with ulcerative colitis who require surgical intervention are those in whom the disease can be termed intractable. These are the patients who have repeated exacerbations of the disease to the extent that they are chronic invalids; it is impossible to maintain their weight; frequent stools of pus, mucus and blood occur, perhaps with incompetence of the anal sphincter; they cannot be gainfully employed and are economic cripples. They have usually had all types of medical therapy and are hopelessly discouraged. It is in this group that the greatest judgment is required to decide upon surgical interference and it is in this group that the combined team who has been following them closely serves a most useful function in outlining treatment.

Since patients with chronic ulcerative colitis are chronically debilitated and represent poor surgical risks, their pre-operative preparation is important. A high caloric diet with supplementary vitamin intake, repeated blood transfusions, adequate fluids, the use of antibiotics and in many a short course of ACTH may be advisable. Based on the experience in this clinic reported by Elliott, Kiefer and Hurxthal (1951) it has been found that temporary and partial remission of symptoms can usually be

obtained with ACTH but that with continuation or interruption of the medication after an appreciable interval the improvement is no longer maintained. For this reason ACTH in our clinic is used primarily in preparation for operation. Failure to prepare patients as well as possible for operation may result in complications with a long period of recovery or even in a post-operative death.

The anæsthesia used in our clinic is spinal Pontocaine glucose anæsthesia usually supplemented with intravenous Pentothal or cyclopropane anæsthesia. For stages of the colectomy, fractional spinal anæsthesia is favoured. This provides the needed relaxation with contraction of the small intestine so that minimum handling is required.

Surgical procedures.—When surgery becomes necessary for patients who have ulcerative colitis only three procedures have merit, and these are ileostomy, partial colectomy and total colectomy. Based on the well-recognized involvement of all of the colon in most patients and the fact that the distal half of the colon and rectum is more seriously involved, lesser procedures are of no value. Experience has shown that temporary or incomplete drainage or diversion by appendicostomy, cæcostomy and colostomy has failed to give more than temporary improvement. In a few patients with the segmental form of the disease it may be so limited that less than total colectomy will be required. For example, the colitis may be confined to the proximal bowel without involvement of the rectum and sigmoid and subtotal colectomy may offer some promise of relief. This may be accomplished by temporary ileostomy which is maintained long enough to obtain clinical improvement, following which subtotal colectomy and anastomosis of the proximal ileum to the sigmoid can be carried out. Rarely, it may be done as a single-stage procedure as a primary resection. When the disease remains confined to the descending colon and rectum, colostomy of the transverse colon can be done together with left hemicolectomy and abdominoperineal resection at the time of the establishment of the colostomy or as a second-stage procedure. In order to be successful with subtotal colectomy the surgeon must make certain that the limits of the resection are in normal intestine not previously involved by ulcerative colitis. Furthermore, it is wise to make the limits of resection at least 12 in. proximal or distal to any point of involvement as determined by the pre-operative examination with sigmoidoscopy and barium enema as well as from the operative findings of inspection and palpation of the colon. In our earlier experience we utilized subtotal colectomy more frequently but found a high incidence of recurrence of the colitis in the remaining intestine. The longest that we have observed a patient who had hemicolectomy and abdominoperineal resection who has remained well has been nineteen years. In most of the patients in whom this conservative approach has been used subsequent completion of the total colectomy has been necessary for the relief of recurrent symptoms. This procedure, however, has the merit that ileostomy may be delayed for a considerable period.

In our earlier experience when 25% of the patients were submitted to surgery, no cases were considered suitable for closure of ileostomy with restoration of intestinal continuity. As earlier ileostomy was adopted an attempt was made to close the ileostomy when remission had occurred. Rigid criteria for consideration of closure were established as follows: complete clinical remission of symptoms with no rectal discharge, negative sigmoidoscopic examination and flexibility of the colon as demonstrated by the barium enema were considered mandatory. If these three factors were not present, symptoms recurred promptly. Approximately half of the patients who had closure of the ileostomy had recurrence of symptoms necessitating a second ileostomy within five years. For this reason we think that this consideration should be approached with great caution and that there will be few patients who have had an ileostomy performed who can have it closed.

Similarly, we followed a number of patients with ileostomy for years in the hope that total colectomy would not be required. In view of the fact that complete relief of symptoms was not obtained with sufficient frequency and because of the incidence of malignant degeneration as these patients were followed over many years we have now adopted the policy that, with rare exception, all patients who have had ileostomy will have total colectomy at an elective time. It has always been our practice to complete abdominoperineal resection and not leave the rectal portion in place unless there is the infrequent finding of no rectal involvement.

The operative procedures of ileostomy and total colectomy are usually divided into two or three stages. In the majority, ileostomy should be done as the sole initial procedure. Unless continuing haemorrhage or malignancy is present, colectomy is deferred for three to six months, permitting the maximum clinical improvement that can occur as the result of the ileostomy. For a number of years we have combined ileostomy and colectomy in patients in the chronic stage of the disease, followed in three to six months by abdominoperineal resection making the operative experience a two-stage procedure. Approximately one-third of our patients are so treated. More recently, Gardner and Miller (1951), Miller *et al.* (1949), Crile and Thomas (1951) and Ravitch and Handelsman (1951) have used colectomy at the time of ileostomy as a one-stage procedure, and have included the acute fulminating and toxic cases in this type of operation. Based on our own experience with the utilization of ileostomy and colectomy combined in one stage we believe that this increases the operative risk unnecessarily since the operative mortality in our own hands is doubled by this plan. Two-thirds of our patients have been operated upon in three stages, consisting of ileostomy, colectomy and abdominoperineal resection. It has been our experience that the important factor in the surgical management of ulcerative colitis is to have a well-functioning ileostomy established before the patient is submitted to the more extensive operation of colectomy.

In the seriously ill patients with acute colitis the ileostomy should be established in the simplest manner possible. Usually a loop is brought out, divided and decompressed without attempting to fix it in an elective fashion. Many of these ileostomies later require revision when the patient's condition permits. The ileostomy of choice in better-risk patients is brought out through the right rectus muscle at the junction of the middle and outer thirds at least 2 in. below the level of the umbilicus. This can be done through a stab wound but I prefer to bring it out through the original incision which permits fixation of the mesentery for the prevention of prolapse. Except in acute cases a divided ileostomy is employed, bringing the non-functioning end in the right upper quadrant outside of the rectus sheath. This will be in the line of the transverse incision for the performance of colectomy. The functioning ileostomy projects 1½ in. above the skin and this projecting loop is straightened by division of the mesentery between the second and third arterial arcades. Immediate decompression is essential and is accomplished by a large, soft catheter passed through the abdominal wall. Because of the danger of infection, the distal end of the ileum should not be inverted or dropped into the abdomen unless colectomy is to be done in the near future. We have not utilized a split thickness skin graft as recommended by Dragstedt *et al.* (1941), preferring to have the mucosa of the ileum cover the entire projecting loop.

With proper management of an ileostomy there should be little difficulty with protection of the skin. The decompressing catheter is removed in from four to six days, following which a temporary, flexible plastic bag is cemented to the skin over the sutures. Within ten days a permanent type of bag can be fitted and likewise cemented to the skin. It will be necessary to refit the bag which will be worn permanently within six to eight weeks of the operation when full contraction of the ileum has occurred. Patients are instructed to dilate the ileostomy stoma daily when the bag is changed to prevent contraction at the skin level. The first ten-day period after ileostomy is the critical time in the surgical management of patients with ulcerative colitis. It is during this period while satisfactory function of an ileostomy is being established that disturbances in fluid and electrolytic balance are most likely to occur. Frequent determinations of the serum chlorides, carbon-dioxide combining power and non-protein nitrogen as well as the serum potassium must be taken. Fluid balance charts on these patients are essential. There is an appreciable incidence of post-operative obstruction of the small bowel which must be recognized early and relieved if a fatality is to be avoided.

Patients with ileostomy should be informed of the necessity of reporting early any difficulty with function. Superficial fistulas may develop in the ileum from an ill-fitting bag. If an attempt has been made to fix the ileum in the ileal wall in the abdominal incision, late fistula formation with infection of the incision may occur. If the ileostomy is not dilated for a sufficient period of time, stricture formation may occur followed by a serious train of symptoms. If adequate fixation has not occurred, prolapse or intussusception of the ileum through the ileum is a possibility. At times quite late after ileostomy, copious watery discharge or interference with drainage may occur owing to inflammatory change in the distal ileum in the form of a regional ileitis which is an extension of the ulcerative colitis. Any of these complications makes it necessary to revise the ileostomy, bringing out a higher portion of ileum with removal of the involved portion. Failure to recognize these complications and to correct them may lead to a late mortality even after eradication of the ulcerative colitis.

The stages of the colectomy are usually carried out three to six months after ileostomy has been performed. Usually the right, transverse, and descending colon are removed with implantation of the sigmoid colon in the left rectus muscle which is in the line of incision for the subsequent abdominoperineal resection. The latter is usually done three months after the colectomy. There is no objection to a longer interval between these stages if, because of an educational programme or the necessity for working for an interval, it is advantageous to delay it.

Clinical data.—In a twenty-five-year period from 1928 to 1952 inclusive, 871 patients with ulcerative colitis have been treated at the Lahey Clinic. All have been under the care of our gastro-enterological department and have undergone intensive medical therapy utilizing all the forms of therapy that have offered any promise of relief. Surgical consultations have been frequently used so that combined medical and surgical care has been constantly available. 413 patients have been operated upon, or 47% of all cases. This incidence of operation has gradually increased in the past twenty years from 25% to nearly double that percentage (47%). The number of patients requiring surgical treatment becomes greater the longer the patients with this disease are observed. Of 194 patients operated upon from 1928 to 1946 there were 43 post-operative deaths, or a mortality of 22·2%. This high patient mortality occurred chiefly after ileostomy and was the result of delayed acceptance of surgery. In a six-year period from 1947 to 1952, a somewhat larger group of 219 patients were operated upon with 11 deaths, a patient mortality of 5%. This striking reduction in post-operative mortality reflects the greatly improved management of ulcerative colitis.

Expressing the operative mortality as following the different staged operative procedures points out the fact that if an ileostomy is done correctly, is not followed by complications and functions satisfactorily, the subsequent stages of the colectomy can be done with little mortality. There were 313 operations done from 1928 to 1946 with 43 deaths, or 13·7%. In the more recent period of 1947 to 1952, 545 operations were done with 11 deaths, or operative procedure mortality of 2%.

Ileostomy was performed in 355 patients out of the 413 submitted to surgery. The remaining 58 patients had some type of partial colectomy without ileostomy. From 1928 to 1946, 147 ileostomies

were done with 26 deaths, a mortality of 18%. With the patient mortality reported above for this period of 22·2%, it is clearly demonstrated that in only 4·2% did death follow in any patient having subsequent stages of colectomy. In the later period of 1947 to 1952, 208 patients had ileostomy with 9 deaths, a mortality of 4·3%. Thus in the latter period, 0·7% of patients died following subsequent operative procedures.

Our acceptance of total colectomy, including abdominoperineal resection, for patients who have ulcerative colitis in more recent years is demonstrated by its more frequent utilization during the latter period. Only 78 total colectomies were done up to 1946 and 189 were done between 1947 and 1952, with a total of 267 carried out on 413 patients.

Total colectomy during the last six years was performed in two stages, consisting of ileostomy and colectomy as a first stage and abdominoperineal resection as a second stage in 60 patients, while double that number, or 129, had three stages consisting of ileostomy, colectomy and abdominoperineal resection. The operative mortality following a two-stage colectomy was double that when performed in three stages. This should lead one to do an initial ileostomy in any patient who is not a good surgical risk.

During the past four years partial colectomy has been utilized in 35 patients. In 6 the disease appeared limited to the left colon and rectum and hemicolectomy and abdominoperineal resection was carried out. In only 5 was a segmental form of colitis thought to be limited to the proximal colon in whom it was considered feasible to do subtotal colectomy with anastomosis of the ileum to the sigmoid. 24 patients had ileostomy and removal of the colon with the rectal segment left in place for possible later anastomosis by disconnecting the ileostomy. Based on previous experience we believe that this is an incomplete operation and will probably be followed subsequently by abdominoperineal resection.

Major attention in the surgical management of ulcerative colitis has always been directed to the surgical mortality. It should be recognized that subsequent deaths may occur because of complications such as obstruction or a malfunctioning ileostomy. In the six-year period from 1947 to 1952, during which time 219 patients were operated upon, there were 11 post-operative deaths, or a mortality rate of 5% as previously stated. A follow-up of these patients has been made so far as subsequent mortality goes and 7 deaths have occurred, or an additional 3·2%, making a total early and late mortality incident to the surgical treatment of 8·2%. Most of these deaths were due to a malfunctioning ileostomy or to obstruction.

Surgical treatment offers the only means of relief for ulcerative colitis with complications. Nearly all patients in whom surgical treatment is utilized will require a permanent ileostomy. Fortunately, with increasing experience in the development of satisfactory management of ileostomy with improved devices in the form of ileostomy bags which can be cemented to the skin, these individuals are no longer seriously handicapped. They can be restored to a normal physical, social and economic activity and are no longer an economic burden to themselves or to their families. With improved surgical methods the mortality has been reduced to a reasonable level in spite of the fact that operation must be carried out on seriously ill and debilitated patients. The patient who has ulcerative colitis that cannot be successfully treated medically can be assured that he can be operated upon with relative safety and that most patients can be salvaged even after serious complications of the disease have occurred. The improvement in the surgical management of patients with ulcerative colitis must be considered a major surgical achievement.

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Mr. J. C. Goligher: I shall discuss the recent experiences of my colleagues and myself at St. Mark's Hospital in the surgical treatment of ulcerative colitis. We entirely agree with Dr. Cattell regarding the danger of malignant degeneration in this disease. Thus in 73 cases of colitis coming to routine colectomy and excision of the rectum at St. Mark's Hospital, Dr. C. Dukes found cancer in 6 or 8·2%. As Dukes and Counsell have shown, the predisposition to carcinoma is a continuous process and the incidence of malignant change depends on the duration of the colitis (as well perhaps as on its severity and other factors). If our cases are grouped according to the duration of colitis

TABLE I.—INCIDENCE OF CARCINOMA IN COLITIS PATIENTS UNDERGOING ROUTINE COLECTOMY AND EXCISION OF THE RECTUM AT ST. MARK'S HOSPITAL

	No. of patients coming to operation	No. of carcinomas found	Incidence of carcinoma
With a history of colitis of *less than* 10 *years*..	56	2	3·6%
With a history of colitis of *more than* 10 *years*..	17	4	23·5%
All cases	73	6	8·2%

symptoms, as in Table I, it is seen that most of the malignant growths occurred in those cases with more than ten years' history. It is reasonable to suppose that if this identical series of cases were to live without proctocolectomy for another ten or twenty years—as they might well do after successful ileostomy alone—many additional carcinomata would develop. These could well double or treble the incidence of malignancy which we have so far observed, and we are confident that the danger from this source is vastly greater than the mortality attending colectomy and rectal excision at the present day. We agree with Dr. Cattell therefore that excision of the large intestine is an essential part of the surgical treatment of ulcerative colitis, and, moreover, that this should include also removal of the rectum if diseased, because in several of our cases the growth arose in the rectum.

It is when we come to the timing of the colectomy and excision of the rectum that we differ from Dr. Cattell. Originally we followed his plan of a three-stage operation—ileostomy, colectomy, and excision of the rectum at intervals of three months or so—but more recently, impressed by the work of Gavin Miller and his associates (Gardner and Miller, 1951; and Ripstein, Miller and Gardner, 1952) in Montreal, and Crile and Thomas (1951) in Cleveland, we have been doing primary colectomies and proctocolectomies, simultaneously with the ileostomy. The argument for combining the colectomy and ileostomy is that it removes right away the main site of the disease, the main source of toxic absorption and protein loss, and thereby puts the patient in a much better condition for recovery. Obviously if this argument is sound, it ought to apply with especial force to the very ill toxic cases with fulminating colitis, which hitherto have practically always died whether treated by ileostomy alone or by medical measures. Colectomy may seem a serious addition to ileostomy in these gravely ill patients, but in fact it is not technically difficult—especially if done at this stage when the patients are still very emaciated rather than later when they have put on a considerable amount of weight after ileostomy—nor is it attended by much blood loss or shock. Apart from its possible advantages in the very acute cases, combining the ileostomy and colectomy should be valuable in the more chronic cases as well by expediting the process of surgical treatment. In the past surgery for these cases has often been spun out over a period of nine or twelve months, and has entailed much hospitalization and economic hardship. To be able to concertina the whole process into two months or so—allowing for subsequent excision of the rectum three or four weeks after the colectomy—is a real advance, if it can be accomplished without increasing the dangers. But before describing the results which we have obtained with primary colectomy and proctocolectomy, I should like to discuss some of the technical points associated with these operations.

The incision.—Most of us find a long left paramedian incision satisfactory (*see* Fig. 1); it gives good access to the more difficult splenic flexure and yet is adequate for the hepatic flexure and right colon. Exposure of the flexures is facilitated by tilting the patient to the opposite side in turn, but if one does not have a table capable of a lateral tilt this position can at least be obtained for the more difficult splenic flexure by starting the operation with sandbags under the left buttock and chest, and doing this part of the operation first. The sandbags are then withdrawn allowing the patient to lie flat for the remainder of the operation.

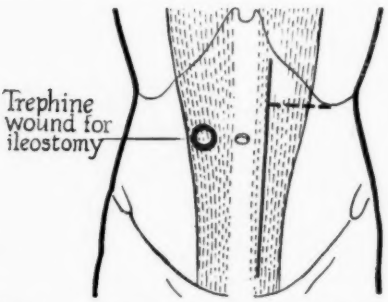
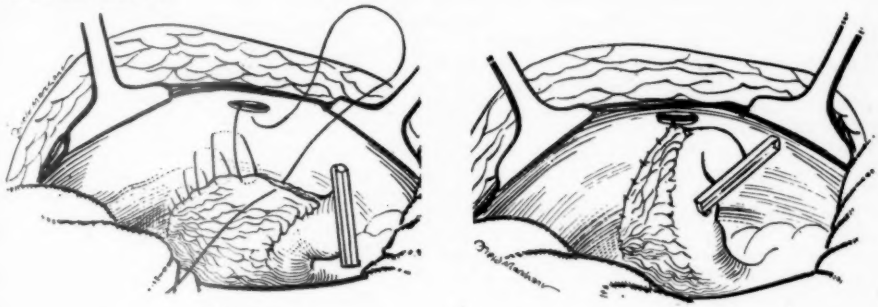


FIG. 1.—Diagram showing incision and site of ileostomy for the operation of primary colectomy.

The ileostomy.—This incision leaves the entire abdomen free for the ileostomy which is established as a separate stab wound with removal of a disc of skin and cutting of the aponeurotic fibres across their long axis. We have generally sited it rather higher than does Dr. Cattell, some 2 in. lateral to the umbilicus (*see* Fig. 1). We close the lateral space on the outer side of the ileostomy as we do in colostomy cases. This is done through the main wound before the ileum is drawn through the abdominal wall. Whilst the assistant strongly retracts the right edge of the main wound, the surgeon views the inside of the right abdomen from the left side of the patient. The cut edge of the ileal mesentery is sutured by means of a running non-absorbable suture to the anterior parietal peritoneum from what

was the right paracolic gutter to the ileostomy stab wound (*see* Figs. 2*a* and *b*). The ileum is then drawn through.



(*a*) (*b*)

FIG. 2.—Closure of peritoneal space on outer side of ileostomy. View obtained by surgeon of inside of right half of abdomen from left side of patient, before ileum drawn through ileostomy stab wound: *a*, Stitch being inserted between cut edge of ileal mesentery and anterior parietal peritoneum from posterior abdominal wall in region of former paracolic gutter to ileostomy wound; *b*, Suture completed. Ileum is now drawn through anterior abdominal wall.

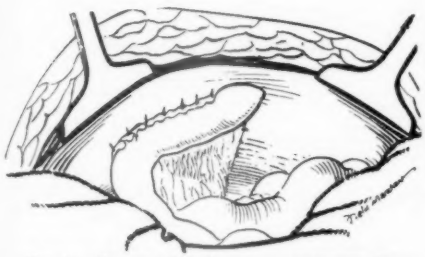
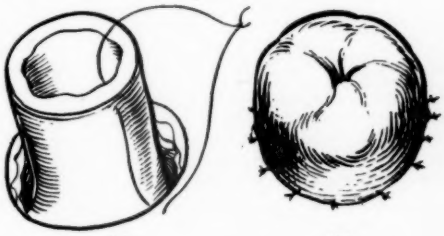


FIG. 3.—Suture of ileal mesentery to anterior parietal peritoneum to prevent prolapse.

Prevention of prolapse.—We agree with Dr. Cattell that direct suture of the ileum to the parietes is to be avoided because of the risk of necrosis with the formation of subcutaneous fistulæ. On the other hand, we have not been able to confirm his contention that suture of the cut edge of the mesentery to the parietes is a certain preventive of ileostomy prolapse, nor, on theoretical grounds, would one expect this step to be really effective because the bowel can always wheel round this fixed point and intussuscept through the ileostomy. What I have been doing recently is to suture the ileal mesentery along a line parallel and close to the bowel for 3 or 4 inches to the anterior parietal peritoneum (*see* Fig. 3), but it is too early to say whether this does any good.

As for the final arrangement of the ileostomy, we used to leave about 2 in. or more of ileum projecting beyond the abdominal skin, and into it a Paul's tube was inserted. Subsequently the protruding piece of bowel was amputated or shrank spontaneously to a projection of 3/4 in. or so with everted mucosa, but with the creation of a ring of fibrosis which often led to stenosis (*see* Fig. 4). Following the advocacy by Patey (1951) of primary suture of the colon to the skin in the creation of colostomies to avoid this stenosis and the application of the same principle by Brooke (1952) in the making of ileostomies, I have been using this particular technique (*see* Fig. 5*a* and *b*). It certainly gives a very nice projecting supple ileostomy which shows no tendency to become rigid or fibrotic. Of course with this method the ileostomy bag has to be applied right away in the theatre.

FIG. 4.—Diagram showing ring of granulation tissue which forms round usual type of ileostomy and which leads to subsequent fibrosis and stenosis.



(*a*) (*b*)

FIG. 5.—Technique of ileostomy with immediate ileocutaneous suture: *a*, Sutures being inserted; and *b*, Final effect with everted end of ileum.

Lastly, I come to the most controversial question in the technique of this operation and that is the *disposal of the rectal stump*. Three or four methods are available:

Firstly, the lower sigmoid may be divided between Zachary Cope clamps and the rectal end brought out as a colostomy through the lower end of the main wound, which is the method we have generally used. This avoids all pelvic dissection and leaves no bowel suture line in the abdomen which might leak. The colo-rectal remnant is removed by abdominoperineal excision three or four weeks later if there are no complications to delay the patient's convalescence.

Secondly, the rectum may be divided and its lower end closed by suture and buried below the peritoneum so that, hopefully, it may eventually be removed by a purely perineal operation. We have not used this method because we have been afraid that the friable diseased bowel might leak and give rise to serious sepsis.

Thirdly, the entire rectum may be removed along with the colon. Undoubtedly if one accepts the principle of primary excision of the toxic diseased bowel in the treatment particularly of fulminating forms of colitis, this is a logical extension of subtotal colectomy, and it must be borne in mind that the rectal segment is often the most heavily affected part of the large intestine, so that its early removal is essential to eliminate toxæmia. Against this step, however, must be weighed the fact that complete rectal excision often entails a considerable amount of hæmorrhage and shock which might prove too much for these debilitated patients. But the very same argument was used to oppose primary colectomy, which we now know is a remarkably safe procedure. We have actually done only 5 primary proctocolectomies, all without a death. But none of these patients was a really acute case. A variant of this procedure designed to avoid the bleeding and trauma of the perineal dissection is to remove the rectum as far as possible from inside the abdomen by an extended Hartmann operation which sometimes takes the excision as far as the ano-rectal ring. We are at present experimenting with this but have only done 3 cases by this method to date, all with smooth recoveries.

Results of primary colectomy and proctocolectomy.—During the past eighteen months the St.Mark's Hospital group of surgeons have performed 61 of these operations with 5 deaths (Table II). This

TABLE II.—OPERATIVE MORTALITY OF PRIMARY COLECTOMY AND PROCTOCOLECTOMY
ST. MARK'S HOSPITAL GROUP OF SURGEONS

No. of patients having operation	No. of hospital deaths and causes		Percentage mortality
61	5	7th day. Peritonitis 8th day. Small-gut obstruction 14th day. Liver failure (cirrhosis) 21st day. P.M. = ? cause 6th week P.M. = ? cause	8·2%

gives an operative mortality of 8·2%. We should like to know, of course, how this figure compares with the mortality in a similar series of patients treated by separate ileostomy and colectomy. Unfortunately our series of cases treated by this latter method extends back to the end of the war and further, to a time when the management of fluid and electrolyte balance was much less accurate and the administration of general anæsthesia less perfect that it is to-day, so that the much higher operative mortality obtained in that series may have been attributable largely to these factors. A valid comparison is thus not possible nor is it reasonable to compare cases treated in different institutions such as St. Mark's Hospital and the Lahey Clinic. All our surgical staff are convinced that the addition of colectomy to the ileostomy has not increased the risks of operation, but on the contrary has made it safer. This is perhaps best shown by the fact that in 19 of the cases in our series of primary colectomies the operation was performed during an acute phase of the disease, in particularly toxic patients, and that all but 2 of these patients recovered, a result which I do not think could have been achieved by ileostomy alone. In fact if simple ileostomy had been the operation in vogue we should have avoided operation at this stage. We are encouraged, therefore, to continue our use of primary colectomy and to experiment further with primary proctocolectomy in the treatment of ulcerative colitis.

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Mr. R. S. Corbett: I wish to confine my remarks to the preservation of the rectum in the treatment of this disease, allowing the patient a return to rectal control after a previous ileostomy.

My experience is based on a small series of 12 cases which have been selected as suitable for this undertaking. I had always been interested in the treatment of this disease, and had addressed this Section from the Chair in 1945, giving a review of the surgical treatment up to that time. (*Proc. R. Soc. Med.*, **38**, 277). As a result I had a series of patients with terminal ileostomies, the first of which was done in St. Bartholomew's Hospital in 1936. Some of these patients were young, and I felt very unhappy about leaving them with permanent ileostomies for the remainder of their lives. In fact, pressure was brought to bear on me by these patients because they were entering the world of

competition and felt that they were severely handicapped. I do not wish to emphasize this because we all know that an adult who has a good ileostomy can carry on a normal life, owing to the great improvement in choice of bag or box which can be offered which he or she chooses to wear. I feel we are greatly indebted to our American colleagues for the Koenig-Rutzen idea of a bag which, in modified forms, is now used by a large number of patients and gives the patient security as well as cleanliness and peace of mind, which they so earnestly seek.

There has developed a growing feeling that the colon—and also the rectum—should be removed even after the great improvement brought about by an ileostomy which up to now has been accepted as the recognized form of treatment. This was founded on the fact that carcinomatous changes were occurring in these diseased colons. I was not convinced that the rectum suffered as much damage as the colon so thought an anastomosis of ileum with recto-sigmoid might well be considered at the time when the colon was being removed.

It was argued that in a disease which usually attacks the rectum first and later spreads into the colon, it was not justifiable to retain that part of the bowel which was first affected and presumably most seriously affected. Also with the increasing evidence of carcinoma developing in such a colon, the safer course would be to make the supreme sacrifice and remove the rectum together with the colon. In theory, this is undoubtedly correct but in practice I have found that in some the rectum is not so seriously affected as other parts of the colon and in others, after ileostomy, the rectum undergoes great improvement as a result of rest.

The fact that the rectum can improve by rest alone is a point in favour of carrying out a terminal ileostomy only in the initial stages of surgical treatment. This course I prefer as a rule, if there is a chance of the rectum being retained. It should be combined with a subtotal colectomy in the very acute cases only.

The definite contra-indications to retaining the rectum are perirectal complications such as, ischio-rectal abscesses, fistulæ and stricture formation—either before or after the establishment of an ileo-stomy.

As a pre-operative indication, the rectum must show signs of only a minor degree of involvement with evidence of healing and absence of gross ulceration or polyposis. This can be assessed by sig-moidoscopy and barium enemata. A mild involvement of the rectum is usually found to respond well to retention enemata of Sulphasuxidine, and a minor degree of polyposis to local cauterization, i.e. after a subtotal colectomy. Cuthbert Dukes has shown that of the three forms of polypoid formation it is only the adenomatous polyp that is likely to become malignant—the other two may disappear spontaneously.

I would like now to refer to my small series. From the summary of 12 cases treated since 1949, all survived the operation (Table I).

TABLE I.—SUMMARY OF 12 PATIENTS WITH ILEO-RECTOSIGMOID ANASTOMOSIS

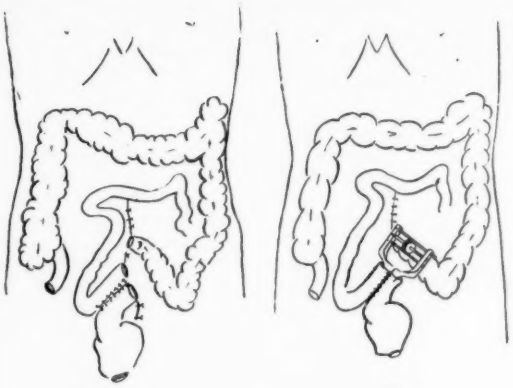
8	Are very well.
2	Show relapses owing to: (*a*) Pyoderma (Case 1). (*b*) Recent diarrhœa (Case 5).
1	Is too recent to assess. Rectal function is established but temporary ileostomy still present and pyoderma healing (Case 12).
1	Died from necrosis of small intestine due to a massive volvulus three months after anastomosis established (Case 8).

Methods.—The method adopted in the majority of this small series was a modification of the original Devine operation, using the spur and enterotome method of anastomosis. Only the first case was treated by the original Devine method (Fig. 1). The stages in the modified form of the Devine method are shown in Figs. 2 and 3. An ileostomy is first established and following this a subtotal colectomy with a temporary ileostomy in the mid-line, subsequently adopting the spur and enterotome method of anastomosis.

Though the use of the enterotome is criticized as being a somewhat slow, and possibly dangerous method of establishing an anastomosis after approximating two portions of bowel together, yet I consider it is a considerably safer method than primary anastomosis. A primary anastomosis is undoubtedly the ideal but in the majority of my patients the condition of the colon, found at operation, was so unsatisfactory that I felt I would be running a grave risk, except in very rare cases.

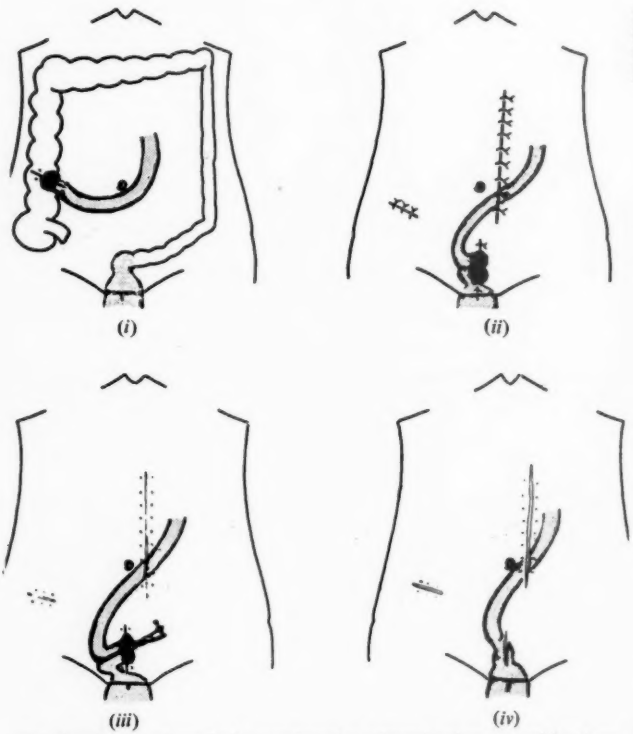
A third method was tried out in the last of the series. Here a primary anastomosis is made between a loop of ileum with the stump of rectosigmoid at the time of the subtotal colectomy and then extending the ileum beyond the anastomosis to form a temporary ileostomy.

It was applied to a patient whose colonic condition, as a result of Dr. E. F. Scowen's care, was very good and the main reason for carrying out surgical treatment was on account of the very severe recurrent pyoderma of the right leg. This gross ulceration completely incapacitated her at that time (Fig. 4). The condition of the recto-sigmoid appeared so satisfactory that I did (with safety) a side-to-end anastomosis of ileum to recto-sigmoid stump following the subtotal colectomy. The whole manœuvre was carried out through a left paramedian incision and my reason for bringing out the ileum as a temporary ileostomy, was to act as a safety valve which it certainly has done. The extraperitoneal closure broke down, which may require further operation. The ulceration is healing but has not yet healed (four months). The rectum is working well.



(*a*) (*b*)

FIG. 1.—Devine's method of colectomy for ulcerative colitis. (*a*) Formation of the ileorectal spur (*b*) Ileo-rectosigmoid septum crushed with an Ochsner-De Bakey spur crusher. (*From* Sir Hugh Devine, *Surg. Gynec. Obstet.*, 1943, **76**, 137.)



(*i*) (*ii*) (*iii*) (*iv*)

FIG. 2.—Stages of surgical procedure for subtotal colectomy with return to rectal control. (*i*) Terminal ileostomy lateral position. (*ii*) Subtotal colectomy with temporary ileostomy. (*iii*) Insertion of enterotome. (*iv*) Closure of temporary ileostomy with return to rectal control.

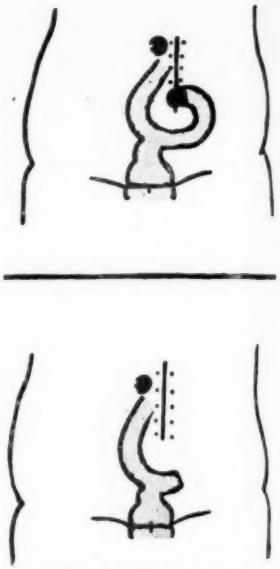


FIG. 3.—Alternative method of ileorectal anastomosis. Stage I, Subtotal colectomy with temporary ileostomy. Stage II, Closure of ileostomy.

FIG. 4.—Left leg of patient (Case 12) suffering from chronic ulcerative colitis and severe ulceration of the leg and dorsum of foot, completely healed after subtotal colectomy.

In the series as a whole (Table II), the first patient illustrates one of the cases where a relapse has taken place. He was the first of 4 young males under the age of 21. They were all worrying about their futures and each in turn came to me for advice. I offered them a return to rectal control and all accepted the offer. The ileostomies had been established four years previously, and the general health of these patients was good. 3 out of 4 cases have done extremely well. The first is now under my care with a recurrence of his severe pyoderma of the right leg. Following the colectomy originally carried out the ulceration had healed, although at another hospital he had had four skin grafts and a lumbar sympathectomy. There was, however, a recurrence of the pyoderma four years later together with the occasional passage of blood *per rectum*. This young man

TABLE II

Patient	Duration before treatment	Treatment	Associated conditions	Remarks
Case 1 P. C. 19	2 years	Skin grafts, &c. Devine op. '48/49	Severe pyoderma. Pseudo-polyposis	*Very well* at first—ulceration of leg healed. Med. studies—*relapse of ulcer of leg* and blood P.R. Now recovering
Case 2 R. D. 17	3 years	(1) Ileostomy '46 (2) Subtotal colectomy '47 (3) Ileo-rectal anas. (Modified Devine '49)	Osteomyelitis R. radius fibula and left arm. Pyoderma	*Very well.* B.O. 3 × D. Married. Perfect health
Case 3 T. W. 17	3 months Fulminating type	(1) Ileostomy '45 (2) Modified Devine '49	Stone in right kidney. Removed successfully between (1) and (2)	*Very well.* B.O. 4-6 × D. "Health could scarcely have been better"
Case 4 B. L. 17	2 years	(1) Ileostomy '45 (2) Modified Devine '49	—	1951 Ischio-rectal abscess recovery 1952 Severe anæmia ? cause 1953 *Very well*—no anæmia B.O. 4 × D
Case 5 K. H. 29	8 years	Modified Devine '50	? Crohn's disease (1) Right hemicolectomy (2) Severe bleeding in bowel	2 years later—*Very well* at first. Adopted a baby. 1 month ago—Relapse *diarrhœa*. No bleeding —losing weight
Case 6 H. M. 36	2 years ? ca.	Modified Devine '50	Previous T. colostomy with resection with hæmorrhages ? ca.	*Very well.* B.O. 3-6 × D
Case 7 Mrs. P. 46	7 years	Modified Devine '50/51	Obstruction in transverse colon. Crohn's disease associated	*Very well.* B.O. 6-8 × D
Case 8 R. H. 16	2½ years	(1) Ileostomy '51 (2) Modified Devine op. 6 months later	Severe pyoderma	*Died.* Very well for 3 months. Strangulation of small gut '52. Massive necrosis. Lived 29 days on terramycin
Case 9 M. O'C. 28	3 years	(1) Ileostomy '51 (2) Modified Devine '52	Pseudopolyposis	*Very well.* B.O. 6-8 × D
Case 10 C. K. 29	10 years	Modified Devine '52	—	*Very well*
Case 11 B. N. 27	5½ years	Modified Devine '52	Double barrelled ileostomy '48.	*Very well.* Was anxious to marry and get rid of ileostomy
Case 12 M. T. 57	12 years	Subtotal colectomy '53 with end-to-side temporary ileostomy	Severe pyoderma left leg	Temporary ileostomy failed to close though rectum working well. Pyoderma healing well

is a very intelligent medical student and felt that it would be wiser for him to make the sacrifice and return to a permanent ileostomy if we would guarantee that his leg would heal. I could not do this. I feared the possibility of involvement of the ileal portion of the anastomosis and not the rectum as keeping up the trouble. We recently had 2 cases where a terminal ileostomy had been established, the point of division of the ileum appearing at that time to be perfectly normal. Owing to an overactive ileostomy and the offensive nature of the discharge later a re-fashioning of the ileostomy was done. In one case 18 in. and in another 4 in. of the terminal ileum was found to be grossly diseased and had to be resected. This made me realize that in these anastomoses it may be the ileum and not the rectum which is to blame. We persuaded this young man to retain his rectum for the present and gave him cortisone. The result was quite dramatic. He started with a dose of 200 mg. daily and is now down to 50 mg. daily and the severe ulceration of his leg is healing rapidly.

The rectal condition shows two ? inflammatory polyps with which I hope to deal at the end of the cortisone treatment. He says his rectum feels better than it has for the last five years. He has two bowel actions a day. The effect of the cortisone is interesting because the usual statement about this drug is that it delays healing; it is certainly not borne out in this case which is quite the reverse.

Another patient was treated with cortisone (not in this series)—one of the most severe cases of ulcerative colitis under our care. Her dermatitis was so severe that this drug was the only one that helped her. Cortisone was also used in the treatment of the last of the series (Case 12). The severe pyoderma of the leg and foot, already shown, healed while under the care of Dr. E. F. Scowen but it broke down again later. As a result she came under my care for colectomy and is now healing.

Our difficulty with cortisone is determining just when to use it! It has been used by us empirically in an endeavour to overcome the complicating factors rather than the colonic lesion.

Case 5 was stated to have suffered from Crohn's disease before coming under our care and a right hemicolectomy was carried out for this disease. Later severe hæmorrhages occurred from the remaining colon and, on investigation, a diagnosis of chronic ulcerative colitis was made and later substantiated by the pathologist after colectomy.

She has had a recent relapse in the form of diarrhœa but no bleeding. Is she behaving like a Crohn's and undergoing further changes in her small intestine? At the present time she is very much better and this is attributed to phenobarbitone.

Case 7 is most interesting in association with Crohn's disease. She had been seen by me at the request of a physician four years previously and a diagnosis of chronic ulcerative colitis was established. She was controlled by medical treatment for four years, when she developed intestinal obstruction due to a stenosis in the transverse colon. The obstruction was overcome by a cæcostomy although at the time of operation she showed the typical signs of Crohn's disease in the terminal ileum, without obstruction. The diseased ileum plus the colon down to the recto-sigmoid was removed. Return to rectal control was carried out by the modified method and she is now very well. The change from one condition to the other appears to have been reversed in this case.

These 2 cases bring up the important relationship between Crohn's disease and chronic ulcerative colitis and there seems little doubt that they are very closely allied.

Conclusion.—I have referred to a small series of cases illustrating the possibility of a return to rectal control after a subtotal colectomy in the treatment of chronic ulcerative colitis. Although the period of follow-up only ranges from four years to a few months, the results are gratifying. 8 of the 12 patients treated are very well indeed and are most grateful.

It is possible that in years to come some of these cases may show recurrence of the disease, or, develop carcinoma in that portion of the large bowel remaining. Nevertheless, I do feel the procedure is justifiable when the only alternative is a permanent ileostomy.

Mr. Stanley Aylett wished to report his experiences with a series of cases of diffuse ulcerative colitis in which the rectum had been preserved, and an anastomosis between the ileum and the pelvirectal region established. He did not believe that, until fibrosis had occurred, the changes in the rectum were irreversible. All had seen cases referred to them by their physician colleagues in which a diffuse ulcerative colitis, involving the rectum as well, had completely cleared following a period of medical treatment.

He suggested that the infection of the rectum might be of a secondary nature, dependent upon the destruction of its protective covering of mucus by the enzyme mucinase, high concentrations of which were continually in contact with its surface. This enzyme was first identified in the stools of patients suffering from ulcerative colitis by Sammons (1951), and it occurs in high titres. Work by Dr. J. H. O. Earle at the Gordon Hospital suggested that its source of origin was mainly in the colon. Certainly it was a fact that, in those cases in which the rectal mucosa had returned to near normal or normal following an ileo-pelvirectal anastomosis the high pre-operative titres of mucinase in the stool had been reduced to very low values or had disappeared altogether. It would seem, therefore, that if the colon is removed the rectum, no longer bathed in mucinase, may recover because its protective layer now ceases to be constantly destroyed.

However much we minimized the disability of an ileostomy there was no doubt that, in spite of the improvements of ileostomy bag design, to many it was a burden difficult to bear. Moreover its establishment was not without its mortality or its morbidity. In advocating a rectum-preserving operation there was nothing to lose and everything to gain. Should the rectal ulceration fail to resolve an abdominoperineal excision could be undertaken and an ileostomy formed. The patient would be subjected to no additional operation compared with the patient upon whom this excision was part of a planned routine treatment of his condition. In 9 cases in which rectal preservation had been carried out resolution of the rectal condition had occurred in 6. These patients were fit and well. They had all put on stones in weight, and were back at work and leading normal social lives. No cases had their bowels open more than eight times in the twenty-four hours and in 2 cases three times was the rule. Anal excoriation was absent. The years of ill-health had disappeared and they were free of any complaint. If this, or even a lesser proportion of cases, can be saved from an ileostomy by initially establishing an ileo-pelvirectal anastomosis the operation is worth performing in those cases in which the disease has not progressed to perirectal suppuration, stricture formation, or the formation of true adenomata.

Mr. Aylett then described his technique: The initial stage of operative treatment consists of laparotomy at which the ileum is divided a few inches from the ileo-cæcal valve and both ends are

closed. The proximal end of the ileum is then anastomosed to the pelvirectal region by a side-to-side anastomosis. The colon is next divided an inch or more above this, and both free ends are exteriorized through separate stab incisions low down in the left iliac fossa. The anastomotic line between ileum and pelvirectal junction is thus provided with a safety valve. Should there be a rise of tension in the rectum, the result either of retained gas or fæces, this increased tension is at once relieved by the escape of some of these products through the exteriorized end of the colon above the anastomosis. The isolated colon is also provided with drainage by means of its exteriorized distal end. The first operative stage is then complete and the abdomen is closed. Some three or four weeks later when the anastomostic line has soundly healed the safety valve colostomy is closed. The colectomy is undertaken when the condition of the patient has sufficiently improved.

In one of his patients, a child of 10 years, in which the first stage of the treatment had been carried out, severe hæmorrhage from the end of the isolated colon necessitated an urgent colectomy before the safety valve had been closed. In a further patient suffering from fulminating ulcerative colitis, with perforation of the colon, a colectomy was carried out and an ileostomy instituted. At a later date the ileostomy was dissected out and its end closed. The small intestine was then anastomosed to the remaining part of the rectum.

Mr. Aylett said that whilst realizing the inevitability of an ileostomy in certain cases he believed that in many efforts should be made to retain rectal function.

REFERENCE

SAMMONS, H. G. (1951) *Lancet*, ii, 239.

Mr. B. N. Brooke said that ileo-sigmoidostomy and ileo-proctostomy could not be considered as routine measures in the treatment of ulcerative colitis. It was perhaps a significant historical fact that excision and anastomosis, which was started as early as 1901 by Lilienthal, was generally superseded by ileostomy and excision in the 1920s to 1930s. Devine's operation had been referred to already but this complex operation was only described by him in 1943 and no account of results has been published by him subsequently. Similarly the account of ileo-proctostomy given by John Devine and Webb in 1951 referred to the technique of the operation as performed in 2 patients without giving long-term results. Best (1952) reviewed patients treated in this way and found that after ileo-proctostomy an average of 5 loose motions are passed each day. The operation, however, could not be entirely dismissed, though the speaker had only been able to anastomose ileum to lower sigmoid in 1 patient out of the 64 on whom he had operated for the disease.

He thought that the suggestion that the disease started in the rectum was pure assumption, possibly arising from the few cases of procto-sigmoiditis which progressed to ulcerative colitis. The disease was usually found in its greatest intensity in the descending and sigmoid colon. Nobody had yet produced any evidence as to the exact site of origin and, indeed, since ulcerative colitis was probably a pathological state due to antecedent trauma to the colon, it seemed unlikely that there was any very specific site of origin.

On the question of the fulminating disease, he agreed with Dr. Cattell's more conservative attitude. There was some confusion about the meaning of the term "fulminating". In America Crile and Thomas (1951) had described this state as being present in any patient with a temperature exceeding 101° F. on several consecutive days in the absence of any complication to account for it. This would hardly even constitute an acute exacerbation in many of the cases he had seen, and certainly not the acute toxic fulminating type which was rare, so rare that, with all due respects to St. Mark's, he doubted whether anyone in this country had performed primary colectomy for it. Primary colectomy was, nevertheless, a sound procedure for an acute exacerbation.

Dr. Cattell in discussing the total mortality following surgery had raised an important point. Since ileitis was one of the causes of death, this brought them to the definition of the disease. There was a form commonly referred to as the "right-sided disease", particularly associated with ileitis, as was noted by Crohn (1949) who differentiated it from the cicatrizing lesion. There was now good reason to believe, from the associated steatorrhœa and macrocytic anæmia in these cases, that it was a primary ileitis and secondary "right-sided" colitis (Brooke and Cooke, 1951). To perform an ileostomy in such cases was to invite further trouble above the ileostomy, since the primary lesion remained in the small bowel. By differentiating this disease from true ulcerative colitis, they would achieve better results.

Mr. Aylett had suggested that mucinase was eliminated by resection of the colon, but Sammons had recovered this enzyme from the small bowel.

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Dr. Cuthbert Dukes said that the pre-cancerous nature of ulcerative colitis was a pathological problem of special surgical interest.

His qualification to speak about this was based on the fact that he had examined operation specimens from more than 20 cases in which cancer has followed ulcerative colitis. In some of these cases malignancy was an unexpected finding, but in others it had been suspected before operation. He pointed out that when intestinal cancer follows ulcerative colitis the malignant tumours are often atypical in appearance and might easily be overlooked, that multiple malignancy is common, and that the carcinomas which follow ulcerative colitis tend to be anaplastic in character and metastasize early. In cases of ulcerative colitis operated on by surgeons at St. Mark's Hospital during the last five years cancer was found in approximately 8%. The longer the duration of symptoms the higher has been the incidence of carcinoma. The average duration of symptoms of colitis before the onset of cancer in this series of cases was fifteen years. This might be called the average incubation period of cancer following ulcerative colitis.

Dr. Dukes said he had compared the incubation period of cancer following ulcerative colitis with that of cancer following familial polyposis, another well-authenticated pre-cancerous lesion, and had found a surprising similarity. A statistical survey of familial polyposis based on the records of 41 families in which there have occurred so far 114 cases of intestinal cancer, had shown that, on the average, cancer was most likely to develop fifteen years after the first onset of symptoms of polyposis. Here was a remarkable coincidence! Cancer following ulcerative colitis and cancer following familial polyposis have a similar average incubation period, namely, fifteen years. Dr. Dukes concluded by saying that his personal opinion with regard to the relationship between ulcerative colitis and cancer might be expressed as follows:

Any patient in whom severe ulcerative colitis has lasted more than ten to fifteen years has entered a phase of life when intestinal cancer has become a serious risk and one which increases henceforth from year to year.

Mr. Clive Butler said that he and others were attempting to identify various clinical and pathological varieties of ulcerative colitis and recently he had read a paper on this subject before the Section of Medicine.

In his opinion there were at least three varieties of colitis: idiopathic ulcerative, right-sided colitis, and segmental colitis.

The first variety had been fully dealt with already; the second variety was very similar macroscopically and microscopically to Crohn's disease and in many cases the ileum was also involved. The right colon was always affected and the disease generally spread distally to invade the descending and pelvic colon.

Diagnosis was established by radiology and the rectum was always normal on sigmoidoscopy.

Mr. Butler then quoted 4 cases he had treated by immediate anastomosis of the normal ileum to the pelvic colon followed by a second-stage colectomy. The first of these patients had been operated on in 1947 and to date all had remained well.

An ileostomy was quite unjustifiable in this group. Segmental colitis was a rare condition and generally simulated a carcinoma or diverticulitis; the treatment was local excision of the affected colon.

REFERENCE

BUTLER, E. C. B. (1953) *Proc. R. Soc. Med.*, **46**, 69.

Dr. F. Avery Jones added some remarks from the viewpoint of a physician. Progress in colitis in recent years had been in four directions. In the first place, there had been an appreciation of the importance of better nutrition. They had got away from the low residue diet, and had placed the emphasis on the positive and important aspect of calories, proteins, vitamins, and electrolytes, particularly potassium, and no doubt this had contributed materially to the improvement in surgical cases.

Secondly, there had been a better appreciation of the importance of the personality of the patient and his reaction to his difficulties, and that was of great help not only to the physician in handling many of these cases, but also to the surgeon, and he thought the most successful surgeons were also good psychiatrists!

Thirdly, there had been improvement in surgery, particularly in the acute cases. He thought that if they considered the acute cases which were going downhill rapidly and carrying a high mortality, any extra assistance—and in recent years they had had that surgical assistance—particularly in the form of simultaneous ileostomy and subtotal colectomy, was very welcome, and he had been impressed with the results in such acute cases.

Fourthly, there had been an improvement in the bag, partly due to the instrument makers. When the bag worked well it worked very well, and the patients seemed to lead perfectly normal and useful lives. This was an important factor when one was considering the question of operation. He had come to the conclusion that there was no patient too ill for surgery. The first case Gavin Miller did in Montreal had seven perforations but recovered. He thought colectomy with ileostomy did better than ileostomy alone. Admittedly their experience with ileostomy was usually at the end of the third or fourth week at least, and it might be that earlier ileostomy which Dr. Cattell advocated was better.

In handling acute cases of colitis one could wait a little while, and he reminded himself of some desperately ill patients in the past who had made a complete recovery. Again, he liked to study the personality of the patient. In some cases the patients were so stable that one was quite happy in tiding them over a fairly long illness. Weight loss and any bleeding must be watched. One could get severe distension of the bowel and this was another indication for colectomy.

One other aspect, not touched upon that evening, was the importance of getting the assistance of the ex-patients with a successful ileostomy and encouraging them to visit patients in whom operation might prove necessary.

Mr. W. B. Gabriel said that they had all admired Dr. Cattell's presentation of the subject and his impressive figures. There was one question that he wanted to ask Dr. Cattell, and he did not think anybody in this country could provide the answer. Most of them had not been doing total colectomies for chronic ulcerative colitis for more than five years. What was the expectation of life of patients who had a total colectomy? Did they make "old bones"? What was the expectation of life in patients who had a total colectomy done before the age of 30 as so many of them were? Dr. Cattell had mentioned that these colectomy patients were rather subject to small intestinal obstruction and internal strangulation, and he himself had had some unpleasant incidents of this nature, for which the abdomen had had to be reopened at varying times after the colectomy and the obstruction relieved. It was his very distinct impression that the development of adhesions had been very much less when total colectomy was done in two stages than when the 3-stage procedure had been adopted as it had been in his earlier series.

For the most part patients who had had a total colectomy achieved a remarkably good measure of health; they were bright, cheerful and active members of the community freed from a life of invalidism, and he himself had never heard a grumble from any of his patients or the wish expressed that they had never had a colectomy done.

Mr. Corbett had mentioned that one of his patients had adopted a child, but this was outdone by a patient of the present speaker on whom he had performed ileostomy, subtotal colectomy and perineo-abdominal excision of the remaining recto-colic segment, the last operation having been done in July 1950. In January 1953, she was seen and found to be in the later months of pregnancy, her age then being 32. He sent her to see Mr. W. R. Winterton at the Middlesex Hospital, who took a great interest in these difficult obstetric cases, and in due course she was safely delivered of an 8 lb. baby boy. He was bound to say that at first she was not such a happy, contented patient as she had been before, but she had gradually got used to her new responsibilities and in a few months' time was quite cheerful and delighted with her baby, a very healthy child.

His experience of total colectomy was limited to 51 cases—31 after a 3-stage operation, 15 after a 2-stage operation, and 5 were what might be called "disrupted Devine's". In all of these cases the final operation was a perineo-abdominal excision and was done blind from below, taking the mobilized rectum upwards. There was no mortality after this procedure, and with one exception all the patients at the time of speaking were alive and well, that is, 50 out of 51. The one patient who had subsequently died had had his last operation done in May 1951 and remained alive and in good health until March 1953, when he developed an acute fulminating septicæmia of an obscure nature associated with a hæmorrhagic rash and died within twenty-four hours.

His experience of Devine's operation consisted of 6 cases of chronic ulcerative colitis, all carefully chosen by reason of the apparent freedom from rectal involvement. There was one death from internal strangulation which appeared to be one of the dangers of this operation. In the remaining 5 cases the crush anastomosis between the ileum and the lower pelvic colon was successfully effected with restoration of rectal function and later closure of the abdominal fæcal fistula. These patients remained well for a time varying between one year and four years after the operation, but in all of these 5 cases a recurrence of symptoms finally ensued—severe perianal and perirectal suppuration in 2 cases and acute flare-up of the rectal ulceration in 3 cases, 1 being associated with very severe hæmorrhage. This last patient went downhill in a most alarming way and had to be built up by blood transfusions, then a perineo-abdominal excision was done and a terminal ileostomy established. The patient was now well and was thankful to have his ileostomy and to be free from all his troubles. He (Mr. Gabriel) was thankful also to think that he would never do another Devine's operation, and it would appear that the odds against this manœuvre being successful were very high. Kiefer and Jordan (*Trans. Amer. Proct. Soc.*, 1946, p. 488) estimated that in a large series of 430 cases of chronic ulcerative colitis the rectum was involved in 94% of cases, and those surgeons who are thinking of trying to preserve rectal function should bear these heavy adverse odds in mind.

Mr. A. Lawrence Abel, after thanking Dr. Cattell and recalling his experience of the hospitality of the Lahey Clinic, said that he noticed from Dr. Cattell's figures that they operated on about 50% of their cases—400 out of 800. At the Gordon Hospital in London they operated on about 25%, because of good results under medical treatment. He was entirely in agreement with Mr. Corbett and Mr. Aylett in their plea for making every endeavour to save the rectum. Mr. Aylett had stressed the problem of the irreversible changes which occurred in the rectum.

In recent years they had had cases in which the process appeared at first sight to be irreversible but in which they had managed to reverse it. He pointed out that even a normal rectum left with

nothing passing through it contracts, but that if the rectum was inflamed it became even more contracted and fibrous. They had had several of these cases in which the rectum held only one or two ounces of fluid. After the colon had been removed, they trained the patient to pass a thin-walled rubber bag attached to a gum elastic catheter into the rectum once or, if well tolerated, twice a day. Then using a large glass syringe to dilate the balloon by pumping gradually increasing quantities of water into it. This had the effect of increasing the capacity of the rectum, but might take from three to nine months. When the rectum reached a capacity of 10 to 12 oz., and on proctoscopy was found to be normal, he did the "hook-up" operation between the small intestine and the peritonealized anterior wall of the rectum immediately above the peritoneal reflexion. Many of these patients had had much proctitis and stenosis before treatment. After their diseased colons had been removed and the dilatations carried out, their rectums had improved and become of normal calibre, and after the anastomosis have regained normal function.

He agreed with what had been said about the psychology problems attendant on these cases, and it was important for complete confidence to exist between patient and surgeon.

Mr. Aylett was doing extremely good work at the Gordon Hospital. Even if, in the future, the condition did recur, provided the rectum had been retained there was still the possibility of removing any newly diseased small intestine, and still retaining the rectum, and this should be tried before the irrevocable abdominoperineal excision. He believed these cases should be given X-ray therapy to the affected region to help those which relapsed after a rectum-saving operation.

Mr. C. Naunton Morgan said that most surgeons were on the look-out for cases of ulcerative colitis in which the rectum could be retained and continuity restored by ileo-rectal anastomosis following subtotal colectomy. In his experience, such cases were extremely rare and usually the rectum appeared to take the brunt of the disease.

Two groups of cases that were suitable for restoration of continuity appeared to be patients with regional colitis (including Crohn's disease) in which the rectum was normal or in which the mucous membrane was only slightly inflamed and cases of ulcerative colitis of many years standing which had burned themselves out, leaving a distensible non-inflamed rectum with pseudopolypi higher in the colon.

Mr. Butler had already described cases in the first group.

Mr. Corbett and Mr. Aylett by their continued experience in attempting to conserve the rectum in operations for ulcerative colitis will obtain valuable information regarding the ultimate surgical management of this disease. Only time would tell.

He had the opportunity, on a visit to Australia, of examining patients in whom the rectum had been retained. Sigmoidoscopy in all cases showed an angry inflamed rectal mucosa with undoubtedly very active disease.

Dr. Cattell, in reply, said that the question had been asked whether there were more cases of ulcerative colitis than formerly. In Denmark a few years ago only 132 cases could be collected by Professor Otto Kapel from a number of hospitals. Yet, since this report, many more cases had been observed. A series of cases reported by Mr. Goligher and Mr. Gabriel suggests that more cases are being seen in Great Britain. Mr. Gabriel had enquired about the expectation of life of patients who had total colectomy. They had now followed patients over twenty years who had had ileostomy and total colectomy and who had maintained normal health and activity. The maintenance of proper nutrition was no problem and, indeed, they tended to gain too much weight. Complications as a result of the ileostomy did occur and at times revision of the ileostomy became necessary. Mr. Brooke had referred to a possible definition of fulminating disease. They considered a case to fall in this category if in a first or second attack of acute colitis, the symptoms did not show some amelioration on medical treatment within the first seven to fourteen days. A decision must be reached in these acute cases within this period. Mr. Goligher had referred to prolapse of the ileostomy, a complication that still occurs in spite of a number of technical steps to prevent it. The anchorage of the edge of the incised ileomesentery to the anterior abdominal wall offered the best means of preventing prolapse.

At the Lahey Clinic they had been unsuccessful in attempts to preserve the rectal segment and the attempts reported by Mr. Corbett, Mr. Aylett and Mr. Abel were doomed to failure if their earlier experience with this was correct. Their results were so poor that it had been given up. Continuity of the bowel was preserved only in the segmental form of the disease and in all others ileostomy, total colectomy and abdominoperineal resection were deemed advisable.

From Dr. Avery Jones' comments, in which he supported the co-operative medical and surgical treatment, it is now evident that internists will not continue to insist on continued medical treatment when it can no longer be effective.

Mr. Corbett, in his reply, referred to the great value of a terminal ileostomy as an initial procedure, this allowed rest to the rectum, which is of great value in the recovery of this part of the colon. At any rate, it gave it a chance to be retained. It appeared that in the series reported he had been more fortunate than his colleague, Mr. Gabriel.

The method of Mr. Aylett he felt left rather a long portion of colon behind which was very apt to cause trouble.

Mr. Brooke's remarks were certainly provocative and perhaps a little unkind. The anastomosis of the terminal ileum to the rectum would not be more likely to give rise to a persistent watery discharge than was found in an ileostomy after a period of time. It was well known that the drainage from an ileostomy became quite solid after a time. He did not feel it wise to divide up chronic ulcerative colitis into numerous types as until we knew the cause we did not wish to make it more complicated. If Crohn's disease could be established in the diagnosis, it was certainly not justifiable to carry out the extreme methods of treatment which would be advocated for chronic ulcerative colitis.

Finally, he was pleased to hear Dr. Avery Jones's remarks about the medical care of these cases.

In reply to Mr. Abel, he wished to point out that in the first 4 cases in his series the rectum had been out of action for four years and yet by the aid of retention enemata, the rectum functioned well.

United Services Section

President—Sir STANFORD CADE, K.B.E., C.B., F.R.C.S., M.R.C.P., Hon. F.F.R.

[*June* 10, 1953]

DISCUSSION ON MILITARY MEDICAL PROBLEMS IN KOREA

Major-General A. G. Harsant: *Surgery in Korea.*

At the outbreak of hostilities in 1950 there were no United Kingdom troops in Korea and Japan. The Army of Occupation was mostly American; but there were some Australian troops, including an Australian hospital of 200 beds in Kure, Japan.

When hostilities started, and developed into a United Nations conflict, the overall medical responsibility was American, and this still remains the case, under the United Nations. The United Kingdom and Commonwealth troops, together with the contributions from other members of the United Nations, were built up into this background.

Units of the United Kingdom and other members of the Commonwealth were formed into a Commonwealth Division in 1951, and this Division forms part of the American 1st Corps in Korea.

It must be realized that this one Commonwealth Division is only one of a total of 16 or 17 divisions fighting in this theatre; and, moreover, that in this Division United Kingdom troops form only a part (approximately five Infantry battalions, Tank Regiment, Field Regiment, R.A., &c.). The rest of the Division also includes some Australian battalions and a complete Canadian Brigade, New Zealand Artillery, &c.

The troops comprising the remaining 15 or 16 divisions are largely American, with an increasing number of South Koreans—together with elements from the other members of the United Nations. The South Korean troops are playing an increasing part and already comprise more than one complete division and corps, officered throughout by their own officers.

The complex anatomy of the Force can be appreciated during a visit to the United Nations Cemetery at Pusan: the cemetery is divided into plots for the dead of 21 nations.

Moreover, on visits to forward surgical hospitals, the nationality of the patients seen may be predominantly, or a mixture of, Philippine, Turk, Greek, Ethiopian, Swedish, French, &c., according to the sector of the front on which hostilities have been recently active.

A brief reference to the map will help to show the situation of the American chain of responsibility. Headquarters of the United Nations and of Far East Command U.S.A. is outside Tokio and here the Chief Surgeon (or D.M.S.) has on his staff Consultants in Medicine, Surgery and Orthopædic Surgery. The consultant supervision of all medical units in Far East Command and in this theatre of operations is under this Headquarters. The fighting troops in Korea are integrated into the 8th U.S. Army in Korea of which the headquarters is at Seoul. The D.M.S. (Chief Surgeon) 8th Army, has on his staff Consultants in Medicine and Surgery; theirs is the ultimate responsibility for the consultant supervision of all medical units in the 8th Army.

The American scheme of casualty treatment and evacuation closely parallels ours, but instead of C.C.S., they have developed Mobile Army Surgical Hospitals, originally designed for 60 patients but which, under the present static conditions, have, in some cases, expanded to a capacity of 200 or more. Primary surgery of battle casualties is carried out in these Mobile Army Surgical Hospitals, to which cases may be brought by motor ambulance or by helicopter. After primary surgery, the cases are evacuated the next day by very well-equipped American-built hospital trains, or by air, to evacuation hospitals, e.g. in Seoul. Here they may have their second-stage D.P.S. and eventually be retained in Korea and returned to the fighting line or they may be evacuated direct by air from Seoul to Base hospitals in Japan (Tokio, Osaka, &c.). From here, they proceed, if and when necessary, to the zone of interior by air.

There are special centres for neurosurgery, thoracic surgery, facio-maxillary and plastic surgery and orthopædic surgery in Tokio and other hospitals in Japan. All neurosurgery cases other than South Koreans, may be directly evacuated to and treated in these units, irrespective of nationality, and it is only after the case is fit for evacuation to home hospitals that he is transferred from these American units to a Commonwealth hospital in Japan *en route* for home.

Under present static conditions, i.e. complete air superiority, absence of bombing, uninterrupted helicopter evacuation from right up as far as the forward units, there have been developed advanced neurosurgical centres in the forward MASHs which are doing first-class work.

At another forward MASH is sited a unit for vascular surgery, while a third is devoted to the care and study of hæmorrhagic fever and cold injury cases.

Other nations have contributed medical units to the United Nations Command. Denmark maintains a hospital ship which has done great work as a static surgical hospital off the coast and at times as an evacuation unit. It is not, however, directly connected with the casualties of the Commonwealth Division at present. Sweden maintains a hospital, allocated at present as an evacuation hospital, at Pusan. Norway supplies an advanced surgical hospital—"NORMASH"—which is allocated by the United Nations to 8th Army and 1st Corps and is at present sited near an American MASH close behind the right flank of the Commonwealth Division. The surgical staff of this unit—like those of some Commonwealth Nations—are volunteers, and serve only for about four months in Korea, and thus there are frequent changes in the staff.

Of the Commonwealth troops in this theatre, the C.-in-C. is Australian, and has on his staff a United Kingdom D.D.M.S. The G.O.C. of the Commonwealth Division of 1st Corps is United Kingdom and his A.D.M.S. Canadian. The Officer Commanding the Commonwealth hospital in Japan is United Kingdom. Of the Commonwealth medical troops the forward units include three Field Ambulances—one United Kingdom, one Canadian, one Indian—and a Canadian Field Dressing Station, with an attached Canadian F.S. team.

There are no Commonwealth Corps or Army medical units, the work of which is done by the American MASH and evacuation hospitals.

Back in Japan, the BRITCOM General Hospital was formed by an amalgamation of a 600-bedded United Kingdom hospital with the pre-existing Australian hospital in Kure, Japan. It has, at present, components from Australia and Canada making up a hospital of 1,000 beds.

At present, the officer-in-charge of Surgical Division is United Kingdom, the other surgeons are Australian and Canadian. The United Kingdom also supplies the anæsthetist, radiologist, ophthalmologist and otolaryngologist. The nursing officers, similarly, are United Kingdom, Canadian and Australian.

In order to diminish the number of minor cases from the Commonwealth Division which were evacuated to Japan a small off-shoot from BRITCOM General Hospital has been formed in lieu of a Field Dressing Station, and is sited at Seoul.

It will be seen, therefore, that some of the unusual factors to be considered in this theatre are:

(i) The fact that we have no surgical units between the forward medical units and the hospital in Japan, and

(ii) Difficulties due to the varying length of service of medical officers from the different Commonwealth and other countries, i.e. those from some Commonwealth countries serve in this theatre for six months and from another Commonwealth country or from other United Nations they may serve a tour of only three or four months, so that the turnover is continual and experience varies.

Thus, to summarize the evacuation and treatment of cases from the Commonwealth Division: Ordinary day-to-day surgical consultations and minor operations are sorted out at the Canadian F.D.S. to whose staff is posted the Canadian Field Surgical Team. Battle casualties receive their primary surgery at Mobile Army Surgical Hospitals which, in the case of the Commonwealth Division, may be staffed by Americans or Norwegians. Thence, the minor cases may pass to the Canadian F.D.S. for their secondary suture and retention, or are evacuated with the American cases by ambulance train, or by air, to an evacuation hospital at Seoul where, again, certain minor cases may be transferred to this advanced unit of BRITCOM General Hospital and thence be retained in Korea. The rest of the cases are transferred by air in Royal Australian Air Force planes to Iwakumi, which is the nearest air strip to BRITCOM General Hospital at Kure, and thence by launch across the bay or by rail around the bay to BRITCOM General Hospital. All special cases, such as neurosurgical, are evacuated to and treated in the American advanced neurosurgical units, and thence in the American base neurosurgical unit in Tokio, and are only received in BRITCOM General Hospital when they are ready for transfer back to England, or other Commonwealth country.

BRITCOM General Hospital is a well-staffed hospital, in good buildings. Cases are retained here either until their treatment is completed, or until they are fit for further transfer to the United Kingdom

by air, under the care of the R.A.F.—a journey taking five to seven days. Less frequently, evacuation to the U.K. is by sea, taking five to six weeks.

There are a few special points of which some mention should be made:—

Blood and Plasma Substitutes

In BRITCOM General Hospital we have a Field Transfusion Team and the blood used in this hospital is taken locally from local Commonwealth sources and is available for use either immediately or after very short storage. All the blood used in Korea is from American sources which, for the great part, has been flown from U.S.A. Plasma is available to our forward units, but the need for it is not frequent as blood is available in free supply and dextran has been available to these units for some time. Cases of vascular injury receive their treatment at the American MASH to which the vascular unit is attached.

Cases of traumatic anuria from any part of the front and of any nationality are flown by helicopter to a special centre in an American evacuation hospital where there is a large research team with all the necessary scientific apparatus.

Helicopter evacuation in this theatre is available so freely and is so easy that it is bringing certain problems. One is that the severely injured cases may reach the operating table within half to one hour of being wounded and it has been necessary to warn medical units of this factor so that they do not give the man food or even drink when he is first received in the medical unit—also, it is possible that cases of greater severity may now reach the surgeon which previously would not have stood the journey.

Body Armour

This was developed by the Americans and has been in limited use for some time. In "The Military Surgeon", February 1953, p. 138, it is stated that, in addition to the armoured vest previously in use, there has been developed a similar body armour for the lower torso. The advantages of the armour have been shown to be undoubted, at any rate preventing wounding of the covered portions by smaller metal fragments; but of course there is the disadvantage of the weight, and there must come a point at which the extra weight put on the infantry soldier counterbalances the extra degree of protection.

Surgical Research in the Forward Areas

A considerable and continuous amount of surgical research has been carried out by American surgical research teams working at American advanced surgical centres; and the feeling is that such forward research is here to stay and in the event of an extensive war one hospital, suitably sited, might be designated *in toto* as a research and teaching hospital. The advantages of such research may be three:

(i) Surgical and physiological research directed to the problems of the remaining small group of 1–2% mortality of battle injuries reaching medical units alive.

(ii) A teaching function for medical officers and surgeons posted to the theatre, and

(iii) As a testing ground for new devices, drugs and techniques.

Of the 400,000 Allied casualties in the three years of hostilities in Korea, the British casualties have been about 585 killed, 1,260 missing or captured, 1,900 wounded (*Daily Telegraph*, May 30, 1953).

In comparison, the casualties sustained in the roads of Greater London only, during one year (1952) were 575 killed, 40,000 injured.

Lieut.-Colonel K. P. Brown: *Medicine in Korea.*

From the purely medical viewpoint, the most interesting item in Korea has been the occurrence of haemorrhagic fever. This had been previously described by the Russians and by the Japanese and was first recognized in United Nations troops in the spring of 1951. The next and so far the most severe outbreak was in the fall of that year when over 1,100 cases were seen, by far the majority of these being American. Our total was about 60 cases, so that it is not surprising that the work on this disease is being done by the Americans. This is particularly so now that there is a special hospital in Korea for the reception and treatment of these patients. To this hospital all men suspected of having this infection, no matter what their nationality in the United Nations Forces, are sent as soon as a provisional diagnosis is made.

The infecting agent, considered by the Japanese to be a virus, but now thought likely to be a rickettsia, appears to be conveyed by the bite of a trombiculid mite, which does not leave an eschar. Infection occurs in localized outbreaks, mainly in the front-line troops and those whose work takes them into scrub. There is no evidence of case-to-case transmission. The period of incubation is commonly about two to three weeks but may be a month.

The bulk of the insult to the body falls on the capillary system resulting in capillary dilatation, increased permeability with transudation of fluid from the circulating blood into the loose areolar tissue, especially that of the retroperitoneal tissues where a gelatinous mass may be seen at autopsy.

There is, as the name suggests, a hæmorrhagic tendency. The clinical picture is one of fever, severe headache and retro-orbital pain, backache and abdominal pain, dilatation of the skin capillaries of the face and of those of the soft palate and conjunctivæ. This facial flush, which has something the appearance of a brisk fresh sunburn, is a very constant feature of the illness in the early stages. Later there are hæmorrhagic manifestations of varying degree and kidney damage becomes evident.

The onset of the illness is acute with very bad headache, occipital or frontal—the worst the patient has ever had—and very often severe shaking chills. The temperature rapidly rises to 103° F. or higher and the patient feels very ill indeed. On the second or third day he may develop backache and begin to vomit. Thirst is a feature and too much fluid seems to increase the tendency to vomit.

On the third day as a rule, one may see petechiæ, first in the soft palate, neck, especially in the skin folds, axillæ and palpebral conjunctivæ. In early descriptions of the disease much was made of the cherry red eyes but this sign is not very often seen now, probably because early diagnosis and early admission to hospital have seemed to lessen the severity of the vomiting, which played a large part in the production of the subconjunctival hæmorrhages. It is still a very dramatic sign when it does occur.

From the third day on bleeding may start from anywhere and needle punctures and handling of the patient are apt to result in severe ecchymoses.

During the late febrile stage some œdema of conjunctivæ and periorbital tissues may be seen and it is during this stage that the transudation referred to earlier takes place.

The fever lasts as a rule from three to five days and falls by rapid lysis but in very ill patients it may not fall at this stage and a persistent high fever is regarded as a bad prognostic sign.

With the fall in temperature is associated some degree of hypotension but only in about ¼ of the cases does this achieve significance and in these patients shock may be severe. It lasts from a few hours to two or three days and while it is on severe hæmorrhage may occur. In favourable cases the changes are reversed and the œdema fluid is reabsorbed. Sometimes so much fluid lies in the tissues that when it is reabsorbed pulmonary œdema steps in.

In all cases there is kidney damage. At about the third day the urine starts to contain albumin in quantity and this may appear very suddenly; for instance, in the morning the urine may be albumin free and by the evening it boils solid. At the same time microscopic hæmaturia may be found. This often progresses to gross hæmorrhage in the stage of oliguria, which is the next evidence of renal damage to appear and which succeeds the febrile phase. There is no constant relation between the degree of hypotension and the severity or the duration of the oliguria. Considerable azotæmia occurs in patients who have had no significant hypotension. The oliguria may proceed to anuria and the whole of this stage lasts up to six days. It is succeeded in favourable cases by a diuresis which is always brisk and is sometimes so brisk that intravenous fluids are called for to keep pace with the output and it is not easy to maintain electrolyte balance.

There is a gradual return to normal renal function over the next few weeks and usually by the end of three months the patient is able to concentrate reasonably well—to, say, 1025 after eighteen hours' deprivation of fluids. As far as is known there are no residua of this illness.

Certain of the clinical pathological findings are of some interest and importance.

The albuminuria and the hæmaturia have been mentioned already. The specific gravity of the urine, high at first in the febrile stage, falls and at the onset of oliguria may be no higher than 1010 and at the diuretic stage around 1002–1004. In spite of this low figure the urinary chlorides during diuresis often total 20 or more grammes daily.

The leucocyte count in the early days is normal or low but after the third day it rises to an average figure of 20,000, the main part of the rise being in the neutrophil series with a shift to the left. The highest figure recorded is around 100,000. Counts of this magnitude are regarded as being of bad prognostic significance.

The platelet count is reduced from the third or fourth day and there is also an increased capillary fragility. These changes revert to normal at the stage of oliguria.

Diagnosis in the very early days is not easy for the symptoms at that stage are mostly non-specific. The facial flush and the capillary congestion are a considerable help as at this stage it is only too easily confused with other febrile illnesses which are common enough.

Prognosis: The overall mortality rate is now about 5%. Death may occur from shock, from hæmorrhagic complications, from uræmia, from pulmonary œdema during the time of mobilization of the fluid from the tissues, especially if the patient has been overhydrated in the first few days, and, rarely, from electrolyte imbalance during the diuretic phase.

Treatment: There is no specific treatment for this disease. All the available antibiotics have been tried at all stages without success. At one time it was thought that the use of convalescent serum or whole blood given before the third day was of value but this has now been given up and the emphasis

is on good nursing from the earliest stage of the disease. Because of the difficulty of making a confident diagnosis in the first two days or so those in charge of the hospital ask that any patient in whom there is a reasonable suspicion of this disease should be sent to them. During the outbreak of the autumn 1951 it became obvious that travelling was very bad for these patients with hæmorrhagic fever, and in addition to the formation of the hospital in Korea, the helicopter service was extended to cover them and now they get to hospital within an hour of the diagnosis being made.

Limitation of fluids in the early stages.—Care is taken to maintain fluid balance, erring on the side of too small an intake rather than too great. There is a good deal of evidence that too much fluid early increases œdema, makes vomiting worse and tends to aggravate the shock, besides, as has been said, increasing the risk of pulmonary œdema. Abdominal pain is a feature of variable prominence in the late febrile phase. This is thought to be due to retroperitoneal œdema which appears to be made worse by too much fluid. Fluid restriction, of course, applies with even more force during oliguria and anuria. Some of these patients have been dialysed on the artificial kidney which is functioning with its attendant flame photometer at one of the evacuation hospitals within easy helicopter run of the front line. Here the cases of traumatic anuria are taken for treatment. So far, I understand, no success has been obtained in dialysing patients suffering from hæmorrhagic fever though this is far from true of the traumatic anuria cases.

In the treatment of shock the usual measures are used and in the less severe cases tipping the bed and the use of elastic bandages are adequate. In more severe cases some success has been obtained using salt-poor albumin and by the use of nor-adrenaline.

This is a brief review of some of the features of hæmorrhagic fever. It is based partly on personal experience but I have drawn largely on the knowledge imparted to me by the physicians at the Hæmorrhagic Fever Hospital who were most generous in discussing their work, as indeed they and all their colleagues are in all their dealings with us in Korea.

It is odd that this disease should occur in such quantity in Korea, but that scrub typhus should be limited to the cases described by Mackay Dick and his colleagues in 1951 (*J. R. Army med. Cps.*, **97**, 227). So far as I know no other cases have been described.

Malaria has not been a serious problem for prophylactic Paludrine has been taken with fair regularity. The infections have all been with *P. vivax*. Treatment has been with quinine and Pamaquin. In the U.S. Army they use Chloroquine for prophylaxis—one tablet (0·5 gramme) once weekly—and for treatment, in which also they now use Primaquin.

Apart from the usual upper respiratory tract infections the biggest single cause of wastage has been infective hepatitis. The average time away from duty has been fifty-three days, this including the time spent at a Convalescent Depot after leaving hospital. Here again, where we had hundreds of cases, the U.S. Army had thousands and they were able to conclude that feeding is the most important part of the treatment. It was found that those who took from the start a very high calorie diet took less time to get well than those who fed throughout on the normal hospital diet. It appeared to make no difference to length of illness or to its severity whether the patients were kept strictly at bed rest or were allowed up in the ward.

Japanese B encephalitis has occurred sporadically. In 1951 all U.N. troops were protected against this infection but this was not repeated in 1952.

On the whole the health of the troops has been remarkably good. The practice of Medicine in the Korean theatre has been most interesting. Seoul is the centre of an area of infection with paragonimiasis in the native population and it appears to be a common infection. Patients present with cough and hæmoptysis and the radiological picture is that of infiltration which can easily be mistaken for tuberculous infiltration. The diagnosis can only be made by finding the parasite in the sputum and by repeated examination to exclude the presence of tuberculosis. As this disease is also exceedingly common in Koreans and as they do not commonly remain under observation its exclusion for certain seems to be very difficult.

Major **F. J. Ingham**: *Army Health Problems*

A. Environmental Factors Affecting the Health of Troops

1. Climate
2. Clothing
3. Rations
4. Water Supplies
5. Accommodation
6. Sanitation
7. Insect and Rodent Control
8. Welfare and Recreation

B. Preventable Diseases and their Control

1. Cold Injuries
2. Accidental Injuries
3. Venereal Diseases
4. Malaria
5. Infective Hepatitis
6. Hæmorrhagic Fever
7. Dysentery

Introduction

Korea is a comparatively uncivilized country, ravaged by war, with a population in which disease is rife. Malaria is endemic. Intestinal diseases are frequent and the carrier rate of intestinal parasites is high. Typhus, relapsing fever and encephalitis are all possibilities. Tuberculosis and venereal diseases haunt the urban areas.

In spite of all this, the health of the Commonwealth Troops has been remarkably good, and although a fairly wide range of diseases has been encountered, in the majority of these the incidence has not been unduly high. Accidental injuries and venereal diseases were the only causes of sickness that caused any anxiety, although we had to be constantly on guard against cold injuries, malaria, dysentery and hæmorrhagic fever.

A. Environmental Factors Affecting the Health of Troops

The following is a brief description of the environment in which the troops lived and the other essential factors which contributed to their livelihood.

(1) *Climate* (Figs. 1 and 2).—This ranged from a dry cold winter to a warm humid summer. Spring

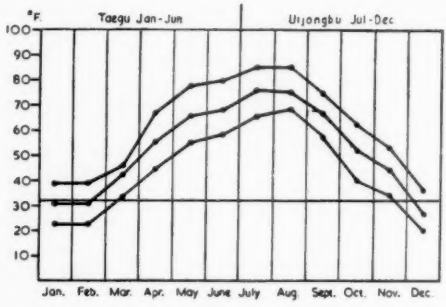

FIG. 1.—Mean temperatures 1952.

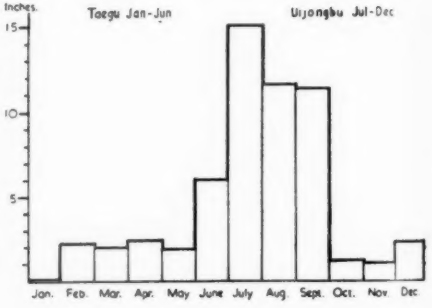

FIG. 2.—Rainfall 1952.

and autumn were mild and pleasant. Unfortunately no temperature records were kept in the Commonwealth Division Area, and the only ones available were supplied by the U.S. Army at Taegu, which is considerably to the South of the combat zone, for the early part of the year, and at Uijongbu, the headquarters of U.S. Army I Corps, covering the later months.

The lowest recorded temperature at Taegu was 11° F. on February 6, but no doubt it was considerably lower in the front line well up North. The lowest recorded at Uijongbu was 4° F. on December 28.

According to the old soldiers who were out in the winter of 50/51, the winter of 51/52 was nothing in comparison, a record for mildness in fact, but no doubt the same story was told to the new arrivals last winter by the veterans of the previous one.

The maximum temperature recorded was 95° F., in July and August.

Mean temperatures are shown on the chart (Fig. 1).

Rainfall was largely confined to the months of June, July, August, and September, reaching its maximum in July (15·18 in.). During the rest of the year it averaged about 2 in. each month, being at its lowest in January. Showers tended to be very heavy while they lasted, rapidly causing a sea of mud.

Unfortunately no records were kept of the relative humidity but this seemed to be at its maximum in July.

It was the general policy not to allow anybody to spend more than one winter in Korea, north of Taegu, and consequently personnel who had spent the six months October to March in Korea would normally be posted either to the southern part of the country or to Japan, where the climate was considerably milder, to complete their tour.

(2) *Clothing.*—It was important that clothing should be supplied which was suitable for the climate just described.

During the winter in Korea, clothing of a special design and scale is worn. This is taken into effect initially in October, and issued by phases up to November. The complete outfit consists of the following garments:

String vest	Peaked cap with ear flaps
Pyjama drawers	Boots cold/wet
Heavy woollen socks (two pairs)	Short puttees or anklets
Flannel shirt	Woollen three compartment gloves
Heavy woollen sweater	Outer glove
Combat jacket and trousers	A lined Parka is worn on top

In the spring, with the onset of warm weather, heavy garments are gradually discarded.

During the summer period, May 15 to September 30, olive drab slacks, flannel shirts and light underwear are worn, with ammunition boots. Shorts are not permitted.

(3) *Rations.*—Special ration scales were designed for Korea, the Cold Climate scale for the period November 1 to March 31 and the Field Service scale for the rest of the year. Both scales consist of a mixture of fresh items of American origin and preserved items of British origin. The calorie value of the Cold Climate scale is approximately 5,100 per day, and that of the Field Service scale 4,500 per day.

The rations have been adequate throughout the year, giving good variety and bulk. The nutritional state of the troops is excellent.

(4) *Water supplies.*—In the forward areas a system of fixed water points was in operation, and there were three of these in the Divisional area. In the rear areas use was made of U.S. Army controlled water points.

The source of water in the Divisional area was either the River Imjin or one of its tributaries. The water in some places tended to be excessively muddy, and sedimentation had to be performed prior to filtration. A high dosage of chlorine, giving 5 p.p.m. free chlorine, is insisted upon by the U.S. Army health authorities, and we generally followed that rule. The high chlorine content was accepted without complaint, and de-tasting tablets, although plentiful, were scarcely used.

Occasionally, for convenience, a unit would use a water supply of its own and in these cases it was found necessary to stress the importance of adequate medical supervision.

(5) *Accommodation.*—In the Divisional area, front line troops live mainly in bunkers dug into the ground, and sandbagged. The degree of comfort achieved depends largely on the individual occupier. In general they are warm, being fitted with some form of space heater, and draught proof, though often rodent infested, and the roof liable to collapse with heavy rain. Also they have a serious fire risk, and there have been many accidental injuries caused through fires, especially among "green" troops.

In the echelon and rear areas, tents, nissen huts and requisitioned buildings are used, the latter being generally in a very bad state of repair. Owing to shortage of engineer services, units have to fend for themselves, and in general they showed sufficient skill and ingenuity to keep themselves warm and dry.

(6) *Sanitation.*—Throughout Korea, field sanitation was used. D.T.L.s were used wherever practicable, and buckets when digging was impossible.

Ablution facilities depended largely on the initiative of units or individuals, and improvised baths and showers were frequently found giving a high degree of comfort. Also, mobile bath units, both British and Canadian, were operating within the Division.

There was a Divisional mobile laundry stationed in Seoul, in addition local native labour was used in unit lines and echelons, and in general these arrangements were satisfactory.

Refuse disposal in the Divisional area has always been a problem. The present ration contains large quantities of tins and containers of various types, and unless a regular routine of refuse destruction is carried out, these tend to accumulate and provide excellent fly and rat breeding places. An intensive campaign was carried on throughout the year, with evidence of marked improvement resulting from it.

(7) *Insect and rodent control.*—Control measures were chiefly directed against the fly, the mosquito, the rat and the field mouse. The latter was considered to be the reservoir of hæmorrhagic fever.

DDT 5% Residual Spray and standard anti-mosquito spray were used against flies and mosquitoes, although on the whole infestation was light. A.L. powder containing 10% DDT was a general issue, but in addition supplies of U.S. Army "Lindane", a powder containing 1% gamma B.H.C. were obtained for use against lice, as lice had been found on North Korean prisoners which were resistant to DDT. This year the Army is being supplied with gamma B.H.C. dispersable powder for residual spraying and a B.H.C. dusting powder of U.K. manufacture.

Fogging and airspray were occasionally used by Commonwealth units, but not as a regular routine. The necessary work was carried out by U.S. Army personnel using their own equipment.

For rodent control, very good results were obtained by the use of Warfarin, an anti-coagulant with no appreciable taste or smell, and therefore a very effective residual rodenticide.

Insect repellents, D.M.P. against mosquitoes and D.B.P. against mites, were used extensively.

(8) *Welfare and recreation.*—Five-day leave periods were granted to all personnel who had been in the theatre for over four months. They would either stay in the Divisional Rest Centre, a short distance behind the Divisional area, or they could be flown back to Tokyo. The latter was, of course, the more popular of the two, though, if the true purpose of the leave was rest and recreation, undoubtedly the Divisional Rest Centre was the more efficacious.

Local amenities in the form of unit canteens and sporting facilities were also provided, often reaching a very high standard under the rather difficult circumstances in which they were conducted. Films and live shows were also in circulation.

B. Preventable Diseases and their Control

Cold injuries (Fig. 3).—During 1952. Cold injuries were rare, the total number of cases being 44,

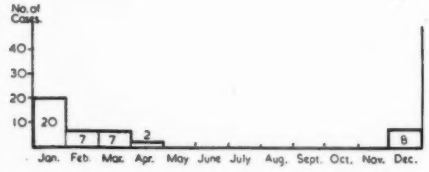

FIG. 3.—Cold injuries 1952 (British Commonwealth Forces). Population at risk 28,000.
Total for 1952=44. Rate per 1,000=1·6.

the maximum number occurring in January. It has been made generally known to all officers that cold injuries only occur when discipline is lax, and the threat of disciplinary action if called for has kept the number of cases small. The present issue of boots and clothing provides adequate protection, and allows for regular changing of socks. Regular foot inspections, the early detection and treatment of hyperidrosis, and the regular use of foot powder have all helped to prevent the occurrence of cold injuries, though constant checks are necessary to ensure that these are being carried out.

(2) *Accidental injury* (Table I).—Accidental injury was the major cause of man-power wastage and was frequently due to carelessness, such as mishandling of firearms, dangerous driving, burns from improvised stoves, and there were a certain number of self-inflicted wounds. A general tightening up

TABLE I.—ADMISSIONS TO MEDICAL UNITS IN KOREA AND JAPAN—U.K. COMPONENT ONLY

Annual Rates per 1,000 *Strength*	1951	1952
Injuries E.A.	85·70	42·67
Injuries N.E.A.	87·00	79·77
V.D. (all cases)	387·03	261·96
Skin conditions	27·24	40·69
Diarrhœa, enteritis and food poisoning	22·63	7·19
Dysentery	5·06	1·12
Malaria (all cases)	4·79	5·55
Infective hepatitis		6·09
Hæmorrhagic fever		2·80
Cold injuries		2·00
Psychiatric conditions	501·75	7·18
Battle exhaustion		0·34
All other diseases		350·20
Total, all causes	1,121·20	807·56

of safety precautions and the enforcement of discipline where applicable will help to decrease these unnecessary losses. Table I shows the U.K. hospital admission rate per 1,000 per annum, and it can be seen that accidental injury holds a high place.

(3) *Venereal disease* (Fig. 4).—The incidence of V.D. in general has been high throughout the year. The principal underlying causes are, the reaction of a young man from the line spending five days' leave in a big city, the civilian attitude in Japan towards prostitution, the accumulation of fairly large

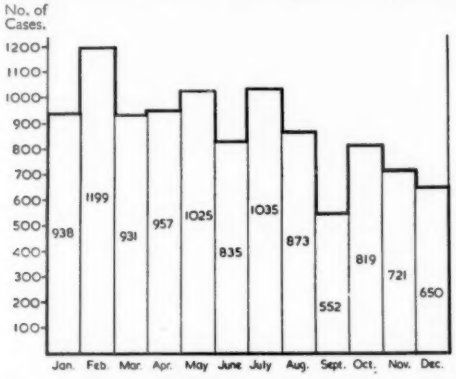

FIG. 4.—V.D. cases 1952 (British Commonwealth Forces).
Total for 1952=10,535. Rate per 1,000=376 overall.
U.K.=264. Canada=616. Australia=386. New Zealand=410.

sums of money while serving in the line, and the general lack of amenities in the way of soldiers' clubs and canteens in the large towns.

The overall V.D. rate averaged 376 per thousand for the year 1952.

Efforts have been made on all sides to educate men in the dangers of these diseases and to discourage them from running the risk of infection. Lectures are given by chaplains, medical officers, and commanding officers. Propaganda films are also frequently shown. Particular attention is directed to newly arrived drafts. It has been found that the incidence of V.D. can be reduced by cutting down to a minimum the periods spent in transit in base towns where the risk of infection is high.

The usual means of individual protection have also been provided.

(4) *Malaria* (Fig. 5).—Korea is not a highly malarious country, and Japan is now considered to be free from endemic malaria. The only known vector in Korea is *A. hyrcanus sinensis*, which breeds freely in paddy fields and paddy ditches throughout the country. There is obviously a fairly large

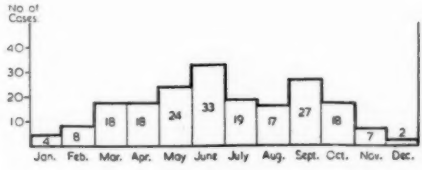

FIG. 5.—Malaria cases 1952 (British Commonwealth Forces).
Total for 1952=195. Rate per 1,000=7.

reservoir of infection among the native population, although to date no figures are available to indicate to what extent the disease is endemic.

The only type of parasite encountered has been *P. vivax*. A few cases occurred during the months of January and February, but began to appear in more considerable numbers in March (18) reaching the peak in June (33) by which time newly acquired infections were also beginning to appear. There was another peak in September (27) since when the numbers have gradually fallen off.

Suppressive Paludrine (1 tablet of 100 mg. daily) was instituted in mid-March owing to the early hatching of mosquitoes in the Divisional area. Civilian labourers and other workers employed by army units in Korea were given suppressive mepacrine (1 tablet daily) over the same period.

(5) *Infective hepatitis* (Fig. 6).—Cases of infective hepatitis have occurred constantly throughout the theatre during the year, the incidence being slightly higher in Korea than Japan as far as U.K.

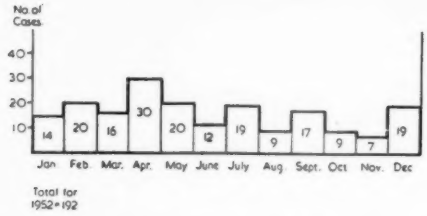

FIG. 6.—Infective hepatitis cases, 1952 (British Commonwealth Forces).
Total for 1952=192. Rate per 1,000=7.

troops were concerned, though the opposite was found among other Commonwealth personnel. No new epidemiological factors have come to light.

(6) *Hæmorrhagic fever* (Fig. 7).—Cases of hæmorrhagic fever occurred during the year in two waves, one with its peak in June, the second with its peak in late October. The U.S. Army had the same

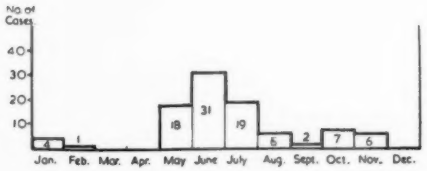

FIG. 7.—Hæmorrhagic fever cases, 1952 (British Commonwealth Forces).
Total for 1952=94. Rate per 1,000=3·4.

experience. Total cases for the year were 94 with 3 deaths, giving a mortality rate of 3%. Mortality rate in the U.S. Army was slightly higher.

Infection has been strictly localized to certain areas and in the Commonwealth Forces all cases occurred among forward troops, more commonly among men of the Infantry and Artillery, who spent more time in contact with secondary scrub. Heavy rodent infestation was also found in these areas.

The preventive measures that have been instituted follow much the same lines as those used against scrub typhus, namely intensive anti-rodent measures and the impregnation of clothing with D.B.P. as mite repellent. Early diagnosis and rapid evacuation contributed very largely to the comparatively low mortality rate.

(7) *Dysentery* (Table I).—Dysentery was a disease we originally expected to encounter in large quantities, but fortunately the number of clinical cases was very low. Flies were not as common as we expected in the forward area, sanitation was kept up to a reasonably high standard, and one got the impression that Commanding Officers in general were sufficiently hygiene-minded to know how to prevent it.

In conclusion, I would say that we were very fortunate in having such a low disease rate under such conditions. I should like to pay tribute to the unit commanders, who, as a whole, certainly did their duty with regard to the health maintenance of their men.

Section of the History of Medicine

President—

The Right Hon. Lord WEBB-JOHNSON, K.C.V.O., C.B.E., D.S.O., T.D., M.B., F.R.C.S., LL.D.

[*July* 1, 1953]

Pierre Marie 1853–1940

By Professor Sir HENRY COHEN, M.D., D.Sc., LL.D., F.R.C.P., F.S.A.

IT is fitting that in this centenary year of his birth, we should pay homage to Pierre Marie and recall his contributions to medicine and neurology.

Alone, or with his master Charcot, or with his many pupils, native and foreign, it was Pierre Marie who first recognized such syndromes as acromegaly, hypertrophic pulmonary osteo-arthropathy, *spondylose rhizomélique*, craniocleidal dysostosis, hereditary cerebellar ataxia, and peroneal muscular atrophy; he had illuminated in face of the challenge of formidable authority such topics as aphasia, and thereby shaken a complacent satisfaction in accepted contemporary beliefs; he had occupied the famous chairs of morbid anatomy and neurology in the Faculty of Medicine in the University of Paris, and was spoken of by Garrison in the 1929 edition of his *History of Medicine*, Philadelphia, as being with Duchenne of Boulogne and Charcot one of the three greatest neurologists of France. Yet after he died on April 13, 1940, no obituary notice appeared in any medical journal in this country, and until last year, when an issue of the *Revue Neurologique* which he and Brissaud had founded sixty years ago was dedicated to his work, there had been no adequate appreciation either of the man or of his great contributions, not to neurology only, but to many other fields of medicine which his percipient mind was destined to illumine. It is true that his death preceded by a few weeks the tragic fall of Paris but *Nature* had carried in June 1940 a brief notice of J. D. Rolleston, and the *Journal of Nervous and Mental Diseases* one by Adolf Meyer.

FIG. 1.—*Pierre Marie* by Marcel Baschet (By courtesy of Masson et Cie, Paris).

It is nearly thirty years since I first visited Salpêtrière. Kinnier Wilson, one of his former assistants, had given me a card of introduction to Pierre Marie, who was then nearing the end of his rule. The pastel by Baschet (Fig. 1) gives the impression he created. The Slavonic features;

deep-set eyes sparkling with intelligence and shrewdness; strong, authoritative, proudly independent, steely but not arrogant features; the grey square-cut hair and beard, the head thrown back. He gave the impression at first sight of conscious superiority and his welcome appeared somewhat formal and cold, but gradually with increasing association the frigidity melted into a warm affability and it was not difficult then to understand the love and loyalty which his assistants gave him and which led Béhague to confess—"Je lui dois comme on doit à un père". If we compare photographs of a twenty years younger and a fifteen years older Marie the features are the same, though age appears to have mellowed him, and, with the firmer etching of the lines, a smile appears.

The centenary of his birth is a welcome and appropriate occasion to see in perspective the nature and quality of his contributions to clinical medicine.

Pierre Marie was born in Paris between Place de la Concorde and Faubourg Saint-Honoré, which in his infancy was still rural, on September 9, 1853, the year in which Charcot graduated with a thesis on arthritis nodosa. He came from bourgeois stock and was sent to a boarding school at Vauves where he pursued classical studies and was subjected to, and imbibed, a strict military discipline which was to influence profoundly his later life. His father persuaded him to study law and he was called to the French bar but he then turned to medicine which had from the first been his own choice. His maturity brought with it a much wider equipment which included several languages, ancient history, and a deep knowledge and appreciation of art (he made several journeys through Europe) which might well have explained his brilliantly acute powers of observation. Was he not later to say, 'L'aspect, rien que l'aspect suffit un diagnostic"?

At 25 he was admitted to a hospital internship under the then two most distinguished professors of the Faculty of Medicine in Paris—Charles Bouchard to whom Marie owed his interest in pathology, and J. M. Charcot whom Marie idolized and to whom he was successively intern, clinical chief, laboratory chief and private assistant. There were intellectual giants in Charcot's clinic in those days, many of whom have a permanent niche in the history of neurology, yet such were the intellectual qualities and industry of Marie that Charcot's contemporaries are agreed that Charcot looked upon Marie as the best of his pupils.

Marie qualified in 1883 with a thesis on the "Formes frustes of Basedow's (Graves') disease", a classical contribution in which was first described the tremor of thyrotoxicosis. In 1888 he was appointed physician and in 1889 professeur agrégé in the Faculty of Medicine. He gave the lectures on "Diseases of the Spinal Cord" which were published in 1892, and which had the distinction of being translated into English and published, with the papers on acromegaly, by the New Sydenham Society. In 1897, he was appointed to Hospice de Bicêtre which had been founded under Louis XIV, and shared with Hôtel Dieu, Salpêtrière, Saint-Louis, and Charité the distinction of being among the oldest of the famous hospitals of Paris.

Marie continued his clinical lectures in the grand amphitheatre of the Faculty, bringing patients from the Bicêtre. It was thus that most of his contributions to neurology were first made public. At his lectures, delivered with Gallic incisiveness and lucidity, with the lantern as his constant ally, the theatre was crowded.

It was at the Bicêtre from 1897 to 1907 that Marie's main neurological contribution was made. Here he created a department which was soon to become as celebrated abroad as it was in France and was to attract distinguished assistants both from home and abroad. In this he received invaluable help from Georges Guillain.

In 1907, Marie succeeded Victor Cornil in the Chair of Pathological Anatomy in the Faculty of Medicine, which Vulpian and Charcot had earlier held. This led to a reorientation of Marie's main interest. With his assistant, Gustave Roussy, who was to succeed him in the chair, and other pupils he reorganized the methods of instruction, built laboratories, and created a museum. These were his major tasks and although he did not wholly abandon pure neurological research, it was subordinated to other interests. But when he was over 60, Marie returned to neurology, in which his most lasting and personal contributions had been made and for the study of which he had no superior and few peers. In 1917, after the death of Dejerine, he was appointed to the Chair of Clinical Neurology in Salpêtrière, so returning to the same service in which he had worked with Charcot forty years earlier. But the times were not favourable for major research. The First World War was not ended and demanded both men and materials. Yet the opportunities which the tragedy gave were not unheeded; important observations on wounds of the nervous system were made with Henri Meige, Charles Foix, Bouttier, Béhague, and Chatelin.

After the war, until he retired from Salpêtrière in 1925, Marie's pupils and collaborators included Abrami, Madame Athanassio-Benisty, Bertrand, Couvelaire, Crouzon, Faure-Beaulieu, Girot, Gougerot, Joltrain, Mathieu, and Sainton. Among the distinguished neurologists from abroad who came to work with Marie at Salpêtrière were Percival Bailey of Chicago, van Bogaert of Antwerp, Bremer of Brussels, van Gehuchten of Louvain, and Boven of Lausanne.

His departure from Salpêtrière in 1925 was in keeping with the man. He uttered no farewell address to his beloved Charcot's clinic and he disappeared without giving those to whom he was Master an opportunity to show their love and admiration. The explanation may well be found

in a previous tragedy. His zest in life had been assailed earlier. At first, although he shunned the expansive social occasions, he did hold simple receptions for his students and assistants in his own home—his wife proving the perfect hostess. His interest in art and his acquisitive instincts were fostered and he wisely mingled work and play—he adored hunting and his other favourite pastimes were fencing and golf. He had two children—André and Juliette. Nothing was wanting—eminence in his profession, wealth, absorbing interest in work and play, perfect domestic bliss. Then Juliette died of appendicitis. His grief was overwhelming and was not assuaged by time. He was seen less and less frequently at both social and professional gatherings.

For a few years he lived contentedly and in 1926-8 his collected works, *Travaux et Mémoires*, appeared. He spent the winter on the shores of the Mediterranean, at the white house of "St. Pierre des Gravettes" at Pradet on the Côte d'Azur; the summer was passed at his estate in Normandy on the Channel in a house where *Les Cloches de Corneville* had been written. His visits to Paris were infrequent but he occasionally attended meetings of the editorial board of *Revue Neurologique*, staying at a hotel in Rue de Lille.

Then tragedy struck deep. He lost first his devoted wife, from a scratch on the thigh which led to an uncontrollable erysipelas; then his only son, a doctor who was studying botulism at the Pasteur Institute succumbed, at the age of 38, to this terrible infection. Marie had lost his wife and children; his sole comfort and consolation were his three grandchildren. He now received only his more intimate pupils. His mind remained clear but he walked with increasing difficulty and pain, until he was almost confined to a wheel chair. Paris saw him less and less.

When Georges Guillain visited him for the last time in July 1939, Marie was deeply distressed. He realized that war was inevitable and the future of France was dark. A little later he complained of abdominal discomfort which worsened. He came to Paris and there was operated on by de Martel, one of the last acts of this great patriot before he committed suicide, rather than face the dishonour of an enemy-occupied Paris. But Marie's condition was beyond human aid, and so, condemned to an early death, he returned to his Mediterranean villa where he died on April 13, 1940.

In death, as in life, he disdained public acclamation, honours and titles. He arranged with meticulous care all the details of his funeral and only his grandchildren accompanied him to rest with his own in the vault of Père la Chaise. Thus passed the physical remains of one of the most illustrious of the founders of modern neurology. His durable legacy is my major theme.

Peroneal Muscular Atrophy

Within three years of qualification, Pierre Marie described with Charcot a form of muscular atrophy which appeared to them to present "sufficiently definite and stable characteristics to merit a special description and place in symptomatic groups". They described the classical features of the disease; a peripheral muscle atrophy, slowly progressive, affecting first feet and thighs, and appearing in the upper limbs—first hands and then forearms—several years later; the muscles of the trunk, shoulders and face remain unaffected; fibrillary contractions appear in the atrophied muscles and vasomotor troubles in the affected segments; contractures are rare and sensation usually intact; frequent cramps occur, and the affected muscles show a reaction of degeneration. The onset is usually in infancy; the disease is familial and occasionally hereditary.

Similar cases had been described clinically by Eulenburg as early as 1856, by Eichhorst, Hammond, Ormerod and others, but Marie and Charcot distinguished not only its mode of onset and progression but also that it was not, as previous authors had suggested, myopathic. They wrote, "Is it then a myopathy with which we are dealing? Is it a multiple peripheral neuritis? It must be admitted that the question is especially difficult because cases exist with pain and sensory disturbances; although the hypothesis of a myelopathy appears to us preferable, it seems difficult to be certain". Tooth described the condition in his Cambridge M.D. thesis in the same year and drew attention to similar clinical features.

In the paper of 1886 there were no pathological findings but later Marie, Sainton and Marinesco published the results of several autopsies. These revealed atrophy and disappearance of the large cells of the anterior horn, and a posterior column sclerosis similar to that found in tabes dorsalis. Its relation to the hypertrophic neuritis of Dejerine-Scttas, to the syndrome of Roussy-Lévy and to the hereditary ataxic polyneuritis of Refsum has been widely discussed, but it would appear that peroneal muscular atrophy is an independent syndrome. Later observations which show involvement of the pyramidal tract and even of the cerebellum in typical cases of peroneal muscular atrophy suggest that it might be but a local expression of a more widespread disorder.

Acromegaly

Marie's first independent major contribution was made in the same year when he described two patients with acromegaly and differentiated them from Paget's disease, myxœdema, and leontiasis ossea. It was hinted that he first noticed them in the street, which even if untrue is a tribute to his perspicacity.

Acromegaly held Marie's continuing interest. Modern knowledge of the pituitary stems from his work and little has been added to the clinical picture which he originally gave in his masterly papers of 1886 and 1889: the non-congenital enlargement of the head and extremities (hence acromegaly; ἄκρος, extremity and μεγάλη, great), the big tongue, kyphosis, headache, blindness, thirst, polyuria, glycosuria, impotence in the male and amenorrhœa in the female. At first Marie had no clear conception of the ætiology although he had noted that in the case of Henri Honrot the autopsy in 1882 had revealed an enlarged sella turcica due to a tumour of the pituitary body, the size of a hen's egg. Marie suggested three possibilities: that acromegaly is (*a*) a general disease, like rheumatism; or (*b*) a disease of the sympathetic nervous system; or (*c*) a developmental abnormality; and he inclined towards the last. In 1887, Minkowski published a case showing pituitary enlargement which, on the analogy of the thyroid in myxœdema, he regarded as of possible significance; in 1888, A. Broca described the skeleton of one of Marie's original cases (Héron veuve Beaufils) and noted the expanded sella, and, in 1890, Marie emphasized three constant anatomical findings—enlargement of the pituitary, persistence of the thymus, and hypertrophy of the spinal cord and sympathetic ganglia. He failed to find normal cells in the enlarged pituitary.

In 1891, Marie and Marinesco supported the view that acromegaly resulted from pituitary failure and sought to confirm this by experiment, but their published results in 1892 proved negative since, after destruction of the pituitary, all the cats died rapidly.

Yet this observation is of interest. Charcot tended to despise the experimental and physiological approach to medicine though many decades earlier Magendie had foreseen future trends by declaring that "pathology is the physiology of disease". In his introduction to *A Clinical Treatise on the Diseases of the Nervous System* by M. Rosenthal, Professor of Neurology in Vienna, of which a translation was published in New York in 1879, Charcot wrote: "In any work of recent date upon the pathology of the nervous system we expect to find, in accordance with a very widespread penchant, theories regarding physiological mechanism predominate over the descriptive portions, and even dilated upon at the expense of clinical and anatomo-pathological details—*those true foundations of all solid work in this department.* But the Vienna School is not open to the reproach of having succumbed to these tendencies."

But by 1892, the methods of Claude Bernard were beginning to exert a stronger influence. Marie never warmed to the experimental method. Like Charcot, he stood for clinical experience without always appreciating the limits within which clinical experience works. Hence in the further elucidation of acromegaly he played little part. It was Benda who in 1900 found eosinophils in the tumour tissue of acromegaly, and Erdheim in 1909 who first demonstrated, what was confirmed by all subsequent investigators, that the pathological basis of acromegaly is an eosinophilism (hyperplastic or neoplastic) even when the sella turcica remains normal; the final link in the chain which originated in the clinical genius of Pierre Marie was forged in 1921 when Herbert Evans and Long isolated the growth hormone from the anterior pituitary which produced gigantism in rats.

It is of considerable personal interest that the first case of attempted surgical relief of acromegaly based on the presence of a pituitary tumour should have been recorded by two of my predecessors on the staff of the Liverpool Royal Infirmary, Richard Caton and Frank T. Paul (the inventor of Paul's tubes). In the *British Medical Journal* for 1893 (vol. ii, p. 1421), they describe and portray a woman aged 33 with typical acromegaly, first seen in June 1891. By December 1892 she had, in addition to intense headache and pain in the left face and neck, right optic atrophy and left papillœdema with temporal loss of the left visual field. "There could be little doubt", they write, "that a greatly enlarged pituitary body was causing, directly or indirectly, increased intracranial pressure". After discussion with Victor Horsley, a right temporal decompression was carried out on February 2, 1893. Pain was relieved but blindness advanced and the patient died after two months. At the autopsy, Dr. Hill Abram found the pituitary body enlarged to the size of a tangerine orange, projecting ½ in. above the level of the lesser wings of the sphenoid, and consisting of dark, soft, hæmorrhagic tumour tissue regarded as a round-celled sarcoma.

Hypertrophic Pulmonary Osteo-arthropathy

It was natural that Marie's interest in enlarged extremities should have led him in 1890 to recognize pulmonary osteo-arthropathy and to differentiate it from acromegaly. Although he paid special attention to the clubbed finger ends and the altered shape of the nails, variously described as "hippocratic", "watch glass", or "parrot beak", he described in advanced cases hypertrophic involvement of wrists, ankles, elbows, knees and even the spine. These changes he ascribed to toxic absorption from the respiratory tract though he was ignorant of their pathogenic mechanism.

Other Bone Diseases

Pierre Marie's interest in bone pathology is shown in several publications during the latter years of the nineteeth century. Between 1886 and 1900, he described, in addition to acromegaly

and hypertrophic pulmonary osteo-arthropathy, two new affections of bone—*spondylose rhizomélique* (corresponding to ankylosing spondylitis and known eponymously as Strümpell-Marie's disease) and *hereditary craniocleidal dysostosis.*

Although he had recognized the condition some years earlier, it was in February 1898 that his paper on spondylitis appeared. He defined it as "the coincidence of complete rigidity of the spine with a more or less pronounced ankylosis of the root joints of the limbs, the small joints of the hands and feet remaining unaffected". He emphasized, before radiology was available, the frequent involvement of sacro-iliac and hip-joints. He did not consider it a form of acute rheumatism or of chronic deforming rheumatism (arthritis deformans), and he distinguished it from hereditary and senile kyphosis. In his view, the affliction was almost invariably infectious in origin, and often gonococcal. He noted the tendency to osteoporosis and the ligamentous ossification which later led Lawford Knaggs to coin the name—spondylitis ligamentosa ossificans. With Léri, Marie demonstrated the anatomical changes which distinguished this from other forms of anklyosis of the spine.

It was in 1898 also that, in collaboration with Sainton, Marie described hereditary craniocleidal dysostosis, a malady in which brachycephaly with delayed ossification of the fontanelles and aplasia of the clavicles are the characteristic features.

Marie emphasized the importance of heredity in achondroplasia, the obstetrical difficulties which arise from the accompanying pelvic deformities and the characteristic "trident" hand.

Hereditary Cerebellar Ataxia

In 1893 there appeared the description of a syndrome to which the eponym, *Marie's cerebellar ataxia,* was later to be attached. In this paper Marie speaks of a new anatomoclinical entity and groups under the title—hereditary cerebellar ataxia—clinical pictures presenting certain common features with Friedreich's ataxia but differing from it in (i) the presence or exaggeration of reflexes, (ii) ocular paralyses and pupillary changes, (iii) visual failure sometimes progressing to blindness, and (iv) onset at a later age. It is not always appreciated that Marie's description of hereditary cerebellar ataxia is not founded on previous personal experience but is based on four previous reports—two from England (Frazer and Sanger Brown) and those of Nonne from Germany, and Klippel and Durante from France. On purely clinical grounds he indicted the cerebellum, and sought thus to unify these heterogeneous syndromes, all related to Friedreich's disease by the common characteristics of their hereditary nature and the presence of abnormal movements. He suggested "that these affections are different forms of the same morbid entity, the same initial process, an hereditary degeneration affecting analogous but distinct parts of the organism". This wide outlook and urge to correlate apparently divergent phenomena revealed that genius in Marie which Delacroix defined as the gift of choice and generalisation. The concept which Marie formulated sixty years ago has many lessons for to-day.

For twenty years Marie remained silent on this topic, though many others, especially Gordon Holmes, had made valuable contributions to our knowledge of cerebellar disease. Then, in 1914, he described, with Foix, 4 patients in three families, who had not only classical cerebellar atrophy but also constant changes in the cord, such as atrophy of Gowers' tract and the adjacent antero-lateral area of the cord, and atrophy of Clarke's column. In 1920, with Foix and Trétiakoff, he published further observations and noted that many patients showed rigidity and a mask-like facies of strial type. Two years later he described, with Foix and Alajouanine, *delayed cortical cerebellar atrophy,* though earlier observations with Crouzon and pathological studies with Rossi had hinted at this syndrome.

Aphasia

Roussy recalls that it was at the Bicêtre between 1901 and 1906 that Marie became deeply occupied in the problem of aphasia and studied with great care the clinical and pathological findings in each case.

Until the beginning of this century, Broca's doctrine, which was the natural extension of the views on cerebral localization first adumbrated by Gull and later by Bouillaud, was almost universally accepted. In his first communication in August 1861, Broca had distinguished clearly between two defects of speech, one associated with the faculty of articulated speech and the other with the general faculty of language. The former he called *aphemia* (*a*, priv., *φήμη* voice), though Trousseau three years later substituted *aphasia* (*a* priv., *φάσις*, speech) since a Greek physician of his acquaintance had told him that aphemia meant "infamous" and had no association with speech defect. The latter is *amnesia verbalis.* The distinction is well described by Head. The general faculty of language is "the power of establishing a constant relation between an idea and a sign whether it be a sound, a gesture, a figure or an outline. If this is destroyed all language would become impossible but this general function may remain intact, the auditory apparatus be normal, all muscles not excepting those responsible for the voice, lips and tongue, may act perfectly and yet a cerebral lesion can abolish articulated speech," i.e. result in *aphemia,* which,

for Broca, had its seat in the 3rd left frontal convolution. Those whom Head, in his monumental work on aphasia, has called the "diagram makers"—Bastian, Ferrier, and Wernicke—soon developed, on scanty pathological evidence, the scheme which persists in our present day textbooks, with motor speech, writing, visual and auditory word centres and their subcortical connexions, the site of lesions being revealed by Beevor's classical questions.

Marie's clinicopathological studies led him to doubt the significance of Broca's area in so-called "motor aphasia", and of Wernicke's zone (the superior temporal and supramarginal gyri) in so-called "sensory aphasia". Yet at first he was reluctant to publish views so diametrically opposed to current teaching. By 1906, however, he was sure of his ground and there appeared from his pen in *Semaine Médicale* three articles on aphasia which were to have the widest repercussions. They came as a bombshell to contemporary neurologists (Head speaks of "Marie the Iconoclast") and were replete with provocative phrases. Their titles were (i) The third left frontal convolution plays no special part in the function of language; (ii) What should we think of subcortical (pure) aphasias?; and (iii) Aphasia from 1861 to 1866—a critical historical essay on the genesis of Broca's doctrine in which Marie showed that by the side of those pathological findings which appeared to confirm Broca's views were many which contradicted them.

Marie's views on aphasia are perhaps best summarized in an article on the function of speech in the *Revue de Philosophie* (1907) in which he replies to criticisms levelled by Grasset:

"i. If the cerebral lesion affects only the zone of Wernicke, clinically there will be found Wernicke's aphasia, pure and simple; internal language (i.e. ideation) only will be affected.

"ii. If the lesion affects only the lenticular zone (or quadrilateral zone, which includes the island of Reil, caudate and lenticular nuclei, and part of the optic thalamus), clinically there will be found anarthria, which is identical with the pure motor aphasia of classical authors.

"iii. If both zones are affected at the same time, Broca's aphasia results."

The formula which summarizes these views is:

Aphasia of Broca = Aphasia of Wernicke + anarthria.

For Marie, Wernicke's sensory aphasia is not of word comprehension only, either by sight or by ear, and there are no areas of cortex whose localized damage produces alexia or agraphia; when Wernicke's zone is destroyed the resulting disturbance extends over a wide range of intellectual functions.

The response to Marie's views was rapid and largely hostile. The Société de Neurologie de Paris, of which Marie was the first Secretary-General, held several special meetings at which many, including Dejerine, Mahaim and Grasset, defended the classical theories. The new doctrine interested many foreign scientists, philosophers and psychologists. Marie reveals himself as a redoubtable polemist in the discussions which are collected in Françcis Moutier's monograph.

Even if we now regard Marie's ideas as perhaps too rigid and absolute, we must concede that they have stimulated newer conceptions and have had a deep influence on subsequent studies on the clinical disturbances of speech.

One of the recurring lessons of science is that until the right question is posed, the right answer is seldom forthcoming. Have we even yet formulated our problems on speech disturbances in terms of normal speech mechanisms, correlating so-called psychological and physiological knowledge? And do we know enough to do so?

Pathological Anatomy

The supremacy of the method of clinicopathological correlation over experiment in the work of Charcot was reflected in the training of his disciples, who were well grounded not only in clinical arts but in pathological techniques. In continuing this tradition Marie made many important contributions to neuropathology. In 1885 he described a new method for the detection of granular bodies which revealed the extent of secondary degeneration. This was an osmic acid technique similar to that of Marchi, and with it Marie studied the degenerations which occur in hemiplegia, in pellagra, in dementia paralytica and combined sclerosis. He showed with Léri that tabetic blindness was due to degeneration of the optic nerve secondary to a localized meningitis. In 1901 he described the cribriform state of the basal ganglia – *lacunar degeneration* – which heralded important work on senile paralyses. Later studies included degenerations secondary to lesions of the red nucleus and peripheral neuritis. With Guillain he emphasized the role of the extrapyramidal tracts, i.e. motor fibres distinct from those of cortical origin, and described hypertrophic degeneration of the olive secondary to a central lesion of the peduncles which led to further observations on the olivary bodies. He maintained, contrary to the views of Beevor and Horsley, and to those anatomists who described distinct territories for the trunk, thigh and foot, that there was no segmentary localization in the internal capsule. Indeed, there are few subjects in this field which Marie or his pupils left unillumined. Many of these together with less important clinical observations, e.g. on the contralateral adductor reflex, are collected with his major works in his *Travaux et Mémoires* (1926-8).

Other Clinical Contributions

Marie was the first to make known in France many clinical entities described earlier elsewhere. These included paramyoclonus multiplex, Thomsen's disease, ophthalmic migraine, hereditary kyphosis, and the cure of myxœdema by thyroid. His description of Paget's disease of bone and neurofibromatosis made these more widely known and he early recognized, in 1920, the sequelæ of epidemic encephalitis, such as Parkinsonism and bizarre movements, which led him to suggest that many of the motor disturbances attributed to hysteria might have an organic basis.

Before the era of neurosurgery he had recognized foraminal crowding as a cause of death in intracranial hypertension and in 1911 he was advocating decompression of the healthy side in selected cases of cerebral hæmorrhage, because operative trauma would thereby be reduced to a minimum and the risk of hæmorrhage spreading to the meninges was considerably lessened.

In the realm of speculative pathology, Marie showed singular prescience especially in regard to the infective nature of certain nervous diseases. In 1885 he supported the theory of the infectious origin of certain infantile paralyses including hemiplegias, and in 1887 he wrote that hereditary cerebral degenerations do not give rise to general paralysis unless they are syphilitic. In 1892 he reaffirmed his belief that infantile paralysis is infective, an opinion which he had held for many years though he adds, "I do not believe it has yet many adherents in France". He had long thought that disseminated sclerosis might follow both known and unknown infections, and maintained that epilepsy was a syndrome, often of infectious origin, and not a disease *sui generis*.

The First World War

The First World War gave a unique opportunity to many distinguished neurologists to study the effects of brain injury and to further our knowledge of so-called cerebral localization. Marie's contributions in this field were interesting but not outstanding. He gave the first description of subjective troubles resulting from head injury and insisted that headaches, changes in personality, insomnia and alterations in memory had a serious and prolonged effect on the victim; moreover he did not believe that this subjective syndrome was wholly psychogenic. In studying, with Chatelin, localization in the cortex he applied a transparent skin to try and determine the site of injury. Though his technique was rightly criticized, it did yield some understanding of cortical localization, especially of the visual fields. He reviewed also the problems of aphasia which led him to doubt the significance of left-handedness in lesions of the right cortex. Other studies included epilepsy, hallucinations and disorientation, and with Madame Benisty he investigated parietal lobe lesions and the associated astereognosis. With Henri Meige, who also died in 1940, Marie studied peripheral nerve lesions and the indications for, and results of, surgical intervention. He took charge of the large centre which was established at Salpêtrière for the treatment of nerve injuries. At the same time he carried out laboratory investigations with Bertrand Trétiakoff which led to a better understanding of degenerations secondary to traumatic lesions of the central and peripheral nervous systems.

I have been able to touch only on the major direct contributions of Pierre Marie to medicine and neurology. I should have wished to say more of his striking and powerful personality which so impressed his students. Outwardly, he was severe and authoritative, preserving the dignity and jealous of the rights of a Chief, but at heart he was warm, sympathetic, affectionate. If he had strict rules for his assistants, it was because he imposed them on himself, and expected from those who worked with him the same industry, zest and conscientiousness. Every communication must be carefully prepared (he wrote out his own meticulously in longhand); he had a profound mistrust of haste and of specious attempts to secure priority. To deserving and promising students he gave unstinted encouragement and support throughout their careers, and in the intimacies of his apartment, first in Boulevard St. Germain and later in the hotel in Rue de Lille, all the outward signs of authority were shed. He disdained titles, honours and decorations, with a contemptuous pride which stemmed not from mock modesty but from a conviction of superiority. He shrank from spectacular social and professional gatherings. But he loved beauty, and his art collections, later to be national possessions, included superb examples of paintings and sculpture of the Spanish school, of the Italian renaissance, and of the Germany of the fifteenth and France of the eighteenth century.

Pierre Marie will live on because of his original descriptions of disease but I should like to believe that two other qualities will add lustre to his memory.

Firstly, as Trotter wrote of John Hunter, "He did not make an epoch, he founded a school". Others of outstanding ability have been content to plough a lone furrow. Marie, like his master Charcot, had selflessly shared his interests and skill with his students at home and abroad; he had fostered in them the urge to advance and spread knowledge. One has but to mention such names as Guillain, Roussy, Crouzon, Sainton, Léri, Lhermitte, Foix, Barré, Bertrand, Abrami, Mortier, Béhague, Rene and Pierre Mathieu, Mlle. G. Lévy, and others of no less renown, in

France; and abroad, Kinnier Wilson of London, Marinesco of Bucharest, van Bogaert of Antwerp, van Gehuchten of Louvain, Percival Bailey of Chicago, Patrikios of Athens, Catola of Florence, Kattwinkel of Munich, Bremer of Brussels, Castro of Brazil and a host of others to appreciate Pierre Marie's influence on the development of neurology in the past half-century.

Secondly, and perhaps of greatest importance, Pierre Marie showed throughout his life an unswerving and fearless allegiance to the pursuit of truth, wheresoever it was to be found, whatever obstacles had to be surmounted, and no matter what personal hurts and frustrated ambitions the defence of truth might carry in its wake. Authority was not for him a sure guide, though he respected it. Let me quote a typical example. He denied the existence of the Aran-Duchenne type of progressive muscular atrophy in a paper in *Revue Neurologique* in 1897 and prefaced his critical and valid thesis with these words. "At the outset, and to prevent any misunderstanding, I will confess that I deeply admire Duchenne of Boulogne, that I look upon him as one of the great patrons of Neurology, 'sed magis amica veritas' "; and he ends this paper by extolling Duchenne of Boulogne who "showed himself in this question of progressive muscular atrophy as always a marvellous observer but who had neither the clinical nor anatomical equipment to make the best of his observations. This does not detract from the merit of accomplishing such a remarkable work. But, however honourable they be, his errors are none the less errors, they belong to history; let us sink them in the light of our present knowledge".

I cannot hope to have done justice to the subject of my theme. Fifty years of productive clinicopathological researches and the bringing to bear of so powerful an analytical mind, encouraged by his early training, on the philosophical questions which these posed, cannot be compressed into a brief address, but I shall have fulfilled my task if I have paid affectionate tribute to one to whom I owe much and whose teaching and writings have been a continuing stimulus to many generations of physicians.

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Section of Pædiatrics

President—D. W. WINNICOTT, M.A., F.R.C.P., M.R.C.S.

[*May* 7, 1953]

Recurrent Generalized Lymphoreticulosis

By ROBERT CLEMENT, B. DUPERRAT, J. GERBEAUX, A. COMBES-HAEMELLE and G. BOUVEAU

WE have been struck by the atypical features and the gravity of a few cases of adeno-splenomegaly. They were characterized by recurrent fever and rashes, mononucleosis in blood and marrow and a prolonged course. We met those cases in boys aged from 2 to 10 years (1953, *Pr. méd.*, **61**, 585). The biological and histological features are rather different from those of the best-known types of acute reticulo-endotheliosis; therefore their classification is rather difficult. We have chosen the title "Lymphoreticulosis" because of the essential lesions, which are hypertrophy and hyperplasia of reticular cells, infiltrated with lymphoid cells; the words "generalized" and "recurrent" emphasize two important clinical features.

The onset is sudden, with high temperature. The fever is irregular, with tachycardia and general toxæmia. There is tonsillitis, a scarlatiniform or morbilliform rash, sometimes with petechiæ, and swelling of the whole lymphoid system. The lymph nodes are enlarged, but isolated, and mobile; they never soften or suppurate. The spleen is considerably enlarged; the liver less so and less often. Tonsillitis may interfere with swallowing. In 2 boys we noted mediastinal adenopathy; in a third X-rays showed diffusely disseminated granulo-reticular shadows in the lungs, but they disappeared in eight days. Damage to intestinal lymph follicles was perhaps the cause of meteorism and diarrhœa in 3 patients. Pains in the joints in 2 boys can be attributed to histiocytomatosis, but we have never seen deformities like those observed in Still's disease.

Mononucleosis and monocytosis are slighter than in infective mononucleosis.

The Paul-Bunnell-Davidson test was negative several times during and after the illness as also were tuberculin tests and blood cultures. The urine was normal.

The pathological and clinical differences would not be enough to distinguish these cases from glandular fever but lymph node biopsy showed in 2 patients a lymphoreticulosis, quite different from infective mononucleosis. Instead of the predominant lymphoid hyperplasia, narrowing of the sinuses by enlarged follicles, and cytoplasmic and nuclear alterations of the infective mononucleosis, there is an intricacy between lymphoid cells and reticular cells, which are turgid and pale, considerable dilatation of the sinuses, and turgescence of endothelial walls.

These lesions slightly evoke Hodgkin's disease, but there are no Sternberg cells, no eosinophilic cells and the blood picture is less disturbed. The complete recovery and survival for at least six years makes the diagnosis of malignant lympho-granulomatosis untenable.

Besnier-Boeck-Schaumann disease has quite different symptoms and lesions.

It is also possible to eliminate malignant reticuloses which usually show predominant localization in an organ or a system such as lungs, skin or bones, and monomorphic reticular hyperplasia of histiocytic, histiomegacaryocytic, and histiosyncytial type. The metastatic and eccentric proliferation and the atypical cells together suggest that these affections are related to neoplastic rather than inflammatory reactions: likewise the Brill-Symmers' reticuloses ending in sarcomatosis.

The acute reticulo-endothelioses in infants published as Letterer-Siwe's disease are a very disparate collection. Most cases are nevertheless characterized by the early age of the patients, hæmorrhage, disorders of blood coagulation, various bone lesions and generally rapidly fatal termination. A certain number of these reticulo-endothelioses are regarded as being the first and non-lipoid stage of Hand-Schüller-Christian disease, and cases have been reported of transition forms between the two affections. The age of our patients, the absence of bone lesions and the complete recovery preclude comparison with these reticulo-endothelioses.

The course of the illness with bouts of fever, rashes, lymph node and spleen enlargement, pains in the joints (noticed in 2 of our patients), and the histological findings in the lymph nodes evoke Still's disease, but none of our patients has ever shown periarticular swelling or characteristic joint deformities.

The Gland Extraction and the Bronchial "Désobstruction" in Some Tuberculous "Primo-infection" Complexes

By P. GIRAUD and H. METRAS
in collaboration with M. Grégoire, H. Giraud, H. Longefait, L. Hartung and A. M. Sanguinetti

PRIMARY TUBERCULOUS INFECTION AND BRONCHIECTASIS

THE authors report cases in which the chain of events between the first tuberculous infection and the bronchiectasis is clearly defined. The history, in these cases, was that of a primary tuberculous infection, with the probable breakdown of a large caseous lymphatic gland, and the establishment of bronchiectasis with or without bronchial stenosis. The surgeon had to carry out excisions necessitated by the complications associated with bronchial dilatation.

In the upper lobe these complications are often late and are usually hæmorrhagic.

In the inferior lobe, the complications develop early and are associated with infection.

GLAND REMOVAL AND BRONCHIAL "DÉSOBSTRUCTION"

At certain periods of this disease, the general tuberculous infection being quiescent, if not altogether healed, the complications that remain are purely mechanical—a consequence of the bronchial occlusion caused by stenosis at the site of the bronchial fistula, or by the caseous material occluding the bronchus.

In 3 such cases, after opening the chest, with careful dissection in order to keep the nerves and bronchial arteries intact, we removed the caseous gland and the material blocking the bronchus, and, after this bronchial clearance, we repaired the stenosed bronchus.

In the 3 cases, we observed the complete disappearance of the atelectasis, and the absence of bronchiectasis. This was confirmed by bronchoscopy.

SIMPLE REMOVAL OF THE GLAND

The last case reported is that of the extraction of a large gland on the point of perforating into the trachea, which was causing severe asphyxia.

Toxoplasmosis and Jaundice of the Newborn

By MARCEL LELONG, LE TAN VINH, G. DESMONTS and D. THOMPSON

THE best-known aspect of toxoplasmosis in the newborn is that of an acute or subacute encephalomyelitis. In our case the clinical picture was primarily a jaundice with hepato-splenomegaly. The condition of the child was serious with œdema, hæmorrhages and signs of hepatic insufficiency, leading to death in fifty-three days. The diagnosis was confirmed by serological tests, by positive animal inoculation and by isolation of toxoplasma.

The infant, D. J. C., was born prematurely at 7½ months. The mother, aged 23, had no illness during the pregnancy.

It is uncertain if the child was yellow at birth, but at 26 hours he presented a frank jaundice. As well as the jaundice the skin showed a moderate cyanosis. The liver and spleen were large, of a firm consistency, and reached two fingerbreadths below the costal margin. Purpura on the limbs and suprapubic œdema up to the umbilicus were also noted.

The skull circumference was 24 cm. (a little large for a premature infant of seven and a half months). The fontanelle was bulging; there was marked muscular hypotonia but there were no other neurological signs. Cerebrospinal fluid: lymphocytes 7 per c.mm.; albumin 700 mg.%. An X-ray of the skull showed some linear arc-shaped calcifications. An air-encephalogram showed deep and wide sulci. The basal cisterna were filled but the ventricles were not visible.

Ophthalmoscopic examination showed: bilateral microphthalmia; corneal opacities; opacities of the lens, but without definite cataract, and evidence of chorioretinitis.

Serological examinations on the 10th day: complement-fixation test for toxoplasma weakly positive in the infant's cerebrospinal fluid; and strongly positive (1 in 64) in the infant's and mother's sera.

There was no Rhesus-iso-immunization and syphilis was excluded.

There was little biochemical evidence of liver insufficiency at one month, but this was marked at seven weeks.

Anæmia was severe at one month, with 2,000,000 red cells and hæmoglobin 40%.

A liver biopsy was done on the 43rd day.

The clinical course was dominated by jaundice which became more and more intense; this was associated with an increase in size and consistency of the liver and the spleen. Somnolence became more and more marked.

After the fiftieth day, the child's condition deteriorated rapidly. The temperature, which until then had been normal, fell to 93° F. Ecchymoses were more numerous and œdema and ascites increased; the to por deepened and the infant died. The jaundice persisted until death. There were never any convulsions.

The autopsy was performed four hours after death.

The body was intensely jaundiced and the skin showed purpura, particularly on the forehead. There was a massive œdema of the legs and genitalia and the abdomen was distended. Some 50 c.c. of sero-fibrinous fluid were in the abdominal cavity. The major changes were in the liver, spleen and central nervous system.

The cerebrospinal fluid was clear and yellow; there was flattening of the cerebral hemispheres and cortical atrophy with bilateral ventricular dilatation. Occasional little whitish nodules were found in the atrophic zones of the brain and there were also some linear areas of calcification. The aqueduct of Sylvius was stenosed. Cerebellum, medulla and cord were macroscopically normal.

Cerebral smears taken at autopsy enabled us to identify typical toxoplasma parasites (Fig. 1).

FIG. 1.—Smear of the brain. Giemsa × 580. Intracellular toxoplasma.

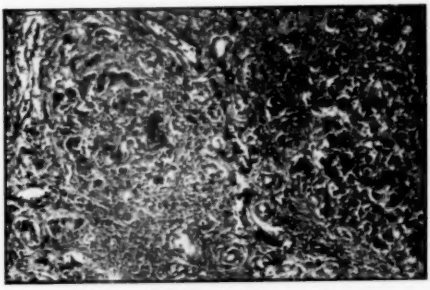

FIG. 2.—Liver. Safran × 109. Pericellular fibrosis.

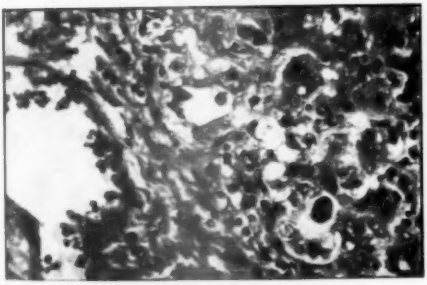

FIG 3.—Liver. Safran × 254. Intralobular bile retention.

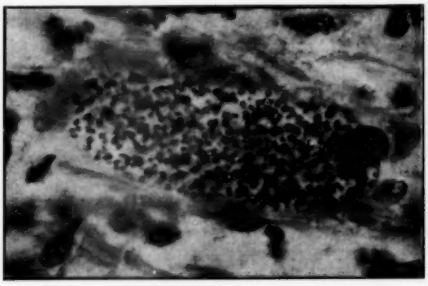

FIG. 4.—Toxoplasma in the myocardium. Silver × 435.

The meninges showed cellular infiltration mainly of lymphocytes, plasma cells and macrophages. There were occasional foci of softening in the cortex and subependymal regions with slight granulomatous inflammatory reaction and some calcification. Granulomata were also seen in the pons, the medulla and the cord.

The aqueduct of Sylvius was blocked with fibrino-cellular exudate which explains the hydrocephalus.

Toxoplasma cysts were seen near the cortical lesions, but not within the granulomata.

Inoculation of the cerebral lesions in white mice enabled us to isolate and to keep the parasite and to maintain the strain.

The *liver* weighed 150 grammes and had an irregular surface and thickened capsule. The parenchyma was firm and dark green, with irregular whitish streaks.

Gall bladder and bile ducts were normal.

Biopsy and autopsy sections of the liver showed lesions similar to those in the brain, but more advanced.

There was marked fibrosis which in some places was portal and in other areas assumed a pericellular arrangement, thus destroying the normal architecture; the hepatic cells caught in this process of fibrosis were atrophic or swollen and multinucleate (Fig. 2).

There was intralobular bile retention, but the interlobular bile-ducts were normal (Fig. 3).

The portal regions contained inflammatory cells, islets of hæmopoiesis and newly formed bile ducts. The extrahepatic bile ducts were normal.

No toxoplasmas were found in the liver.

The *spleen* weighed 90 grammes. It was large and congested and its capsule thickened.

The other abdominal and the thoracic viscera showed no changes other than congestion and occasional purpura. No toxoplasmas were found in any of these organs.

The most striking toxoplasma findings were in the myocardium and striated muscles: There were numerous cysts containing 10 to 30 toxoplasma parasites between the myocardial fibres (Fig. 4). Similar findings were obtained in all the striated muscles studied, including the psoas, pectoralis minor and glutei.

SUMMARY

A case of toxoplasmosis in a newborn infant with icterus gravis is described, the diagnosis having been established by smears, histological sections and by inoculation of mice.

Toxoplasmosis must be considered in the differential diagnosis of pathological jaundice in the newborn, particularly with hepato-splenomegaly. Some similar observations have been recorded in the literature.

Congenital hepatic cirrhosis may be a sequel to toxoplasma infection.

The infection of the baby must be hæmatogenous, that is septicæmic, showing signs of generalized disease, otherwise the finding of lesions in such diverse situations as the central nervous system, liver, heart and skeletal muscles cannot be explained.

This work was done with the aid of the Institut National d'Hygiène (Paris).

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One Hundred Cases of Child Obesity: Some Psychological Data

By R. LAPLANE and M. ETIENNE

BRUCH's theory as to the origin of child obesity has renewed our interest in this subject not only because of its psychosomatic origin but also because of the emotional implications of overfeeding.

Emotionally retarded and socially unadapted, these children seem unable to free themselves from an over-protective mother and indulge in over-feeding to compensate for emotional frustration and to allay their anxiety. They are supposed to be encouraged in doing so by their mother, only too anxious to relieve her own feeling of guilt in this way.

Our inquiries bear on 100 obese children, both male and female, aged less than 15; 9 out of 10 are out-patients of a large non-specialized Paris hospital in a crowded district. We retained only children whose weight was at least 20% above the average; 70% of them exceeded the normal weight by as much as 25 to 75%.

These children have been fully examined both from a biological and a clinical point of view, and no new facts were obtained.

In 60% of cases the obesity started in the very earliest years. Sometimes it could be traced back as early as 6 months.

A psychological study of obese children must take into full account the following points.

It is not an easy matter to decide what is cause and what is effect in child behaviour. Indeed we have often been surprised to note a complete change of behaviour after a child had received a successful but strictly dietetic treatment of obesity.

On the other side the psychological features noted with obese children do not seem very different from those which have been held responsible for other psychosomatic diseases. This lack of specificity may rightly arouse the suspicion: Is there any real disparity in behaviour between obese and normal children?

Our investigation on normal children is still in course of preparation; yet it has already been sufficient to convince us that between an obese child and a normal one, there is no real psychological disparity.

It is true that, in a few cases, we have been able to find perfectly clear evidence of the same psychological profile stressed by H. Bruch.

"Hyperphagie" appeared then to be undoubtedly evidence of a real neurosis; suppressed desires and hidden conflicts were implied. More frequently we found that there was no uniform psychological environment but rather certain dominant features.

For instance a domineering mother and a submissive father are often lacking, the contrary being quite as frequent. Moreover an exceedingly weak mother with a spoiled child is not uncommon. Of these two the child is the bully with a touch of aggressiveness. Finally obese children are far from being always the dull and quiet beings that current opinion would have them. On the contrary, they often display alertness in mind and body, they are playful, outspoken, of the extrovert type.

On the whole, we found it difficult, if not impossible, to individualize a single psychological type; we were content with retaining a few traits which struck us as more common.

In the first place, the tremendous importance of oral activities in these children. Food and all associations related to food range first among their interests. Their cares, wishes and joys are centred on this single trend of thought. Such submission to a purely oral hedonism, to the satisfaction of an elementary need, can rightly be considered as emotional immaturity developed in a favourable family background. In this case prolonged breast-feeding and the ensuing weaning difficulties may perhaps be blamed: 20% among obese children (against 15% non-obese) were breast-fed after the first year.

Again we have been struck by the frequency of over-protective mothers with obese children. This particular relationship creates a typical and lasting closeness between mother and child and it reinforces the interest for food, over-feeding being the result of this complicity. The order of birth among siblings is another interesting item of our inquiry: two-thirds of obese children (against one-third of non-obese) are only children or much younger than the siblings.

Lastly the complete dependence of the obese child on his mother is another remarkable trait. The same passiveness is to be found at school towards his schoolfellows. Physically and morally apathetic, easy-going, fearful, easily influenced, these children are ready to submit to their friends rather than to impose upon them.

It seems obvious that a correlation exists between their attitude towards food and their social behaviour; but it may more aptly be called a tendency than a social inadequacy or neurosis, and least of all a characteristic psychological profile.

It will appear that our discoveries are not so rich as those of H. Bruch; this may be due to the nature of our building material. 40% of the American author's patients were Jews and many were immigrants; their parents had suffered from poverty and undernutrition. Our patients were far from these conditions and, no doubt, the psychological climate is not the same in Paris as in New York.

Before concluding, we cannot overlook an important piece of evidence: all obese children are big feeders, but all big feeders do not grow into obese children. This has been made quite clear in five families of five children or more, all of whom were extremely voracious; only 1 was obese and he ate no more than his siblings.

In conclusion we feel justified in asserting that with regard to obesity, organic factors must not be minimized to the exclusive benefit of psychological features. Child obesity is, no doubt, a psychosomatic disease, but the somatic profile is probably no less worthy of attention than the rather elusive psychological profile.

The Functional Glandular Manifestations of Puberty

By JEAN WEILL
Médecin des hôpitaux de Paris

PUBERTY is an expression of great changes in the physical and psychological balance of the individual. Puberty and the cessation of intra-uterine life at the time of birth are the greatest disturbances that the human organism has to bear. Puberty, like birth, is a period of active endocrine fluctuations more or less harmonious. Though organic disease of endocrine glands is not very frequent at this age, we can often find some purely functional trouble, independent of anatomical changes and usually undergoing spontaneous cure.

Puberty is essentially characterized by a genital maturation, determined not by the formation but by the *liberation* of gonadotrophic hormones, which, as experiment has shown, are pre-existent in the child's pituitary body. The diencephalic mechanism of this liberation is complex and not yet understood.

If we study schematically the principal glandular disturbances we can see that for each glandular function there is closely linked a temporary disorder which can be singled out during the puberty spurt.

It is tempting to speak first of the "hypereosinophilia" of the pituitary body, but we do not dare to recognize a specific physiological change parallel to the specific histological change. We can only say that the somatotrophic hormone, acting on the columnar cartilage, can determine a dysharmonious spurt of growth; the length of the limbs, proportionately short in the young child, seems to become gigantic after a few months. Hands, feet, malleoli, and epiphyses grow rapidly. This ungainly adolescent, who seems perched like a spider on his thin legs, is during this period a relative giant, whose proportions will become, later on, more harmonious. Sometimes, the rapid growth of the nose, the chin, the cricoid cartilage, changes the child's round face in a few months and gives an impression of acromegaly.

Very often these gigantoids are sexually delayed and genital development will be late.

Conversely, retarded growth is sometimes an expression of "pituitary laziness". The lack of somatotrophic hormone is proved by the low level of the blood phosphorus. The delay can also affect the gonads but we are now able to correct the gonadotrophic hormone deficiency. The problem is harder when "chétivism" (under-development) is not produced by glandular trouble, but by the lack of tissue receptivity, which is very often of a nervous origin, and for which, at present, we have no specific treatment.

Thyroid deficiency is often to blame in fat girls, who are slow, apathetic, chilly and seem never to have enough sleep. We cannot say, however, that by contrast there exists a puberal Graves' disease. Sympatheticotonia is the rule during adolescence, and it has been proved by the systematic study of the oculo-cardiac reflex, and by the atropine test. This sympatheticotonia explains why we so often find nervousness, trembling, insomnia, "irritable heart", &c.

Robert Clement describes pulsatile diffuse goitre, with vasomotor and psychic troubles, sometimes even exophthalmos; these are not associated with signs of toxicity; the basal metabolic rate is not high, indeed it may be lower than normal.

All the symptoms are linked to a hypothalamic disorder. They do not amount to those of a true exophthalmic goitre, but slightly suggest that picture. It would be a great mistake to treat them by radiotherapy or antithyroid drugs when sedatives work well.

In the *genital sphere* there occur also temporary disorders of the secondary sexual characteristics, provoking, in the boy, transitory eunuchism, with persistence of the thin skin of feminine type, delay in development of the gonads, and late appearance of hair and beard.

This state is, sometimes, sexually ambiguous, and is reflected in the psychic orientation.

In girls, the slow appearance of sexual maturation can be easily followed by vaginal smears. We have, with Madame Bernfeld, studied it closely. This method can show the very beginning of the genital cycle, at first anovular, just before menstruation. It helps also in the choice of endocrine therapy and its close adjustment to the deficit or excess of œstrogens or progesterone.

The adrenals, whose complete physiology we do not yet know, can be the basis, in the case of insufficiency, of the tiredness, hypotension and hypothermia often described in adolescence. We have tried, in recent years, to work out, more particularly, the transitory hyperactivity of the adrenals. We have described, with Madame Bernfeld, the para-Cushing syndrome, which shows the same temporary symptoms as Cushing's disease, without recognizable organic lesions of the pituitary body or adrenals.

In the study of infant obesity we were struck by the frequency of some of the aspects of hypercorticism and we recognized, in these children, elements of the symptoms described by Albright. The hypersecretion of metabolic steroids gives lipoid anabolism, which provokes face and trunk obesity. Carbohydrate anabolism gives a tendency to hyperglycæmia which can be shown by a test-provoked hyperglycæmia. As for the protein catabolism, although in these transitory disturbances it only rarely causes osteoporosis and amyotrophy, it explains, on the other hand, the striæ we so often find in the obese adolescent when we look for them systematically.

Lastly *hypertension*, which should be under the influence of mineral-corticosteroids, has very rarely been seen in our patients. The hypersecretion of genital steroids is more often manifested by the androgen increase which explains acne in both sexes, and often, in girls, a certain amount of hirsuties, sometimes even virilism, with a harsh voice, and hypertrophy of the clitoris.

In boys, the signs of feminization are not so common. We could, in some cases, recognize an increase of œstrogen by the level of phenol steroids.

In many of our cases, hypercorticism has been proved by biological tests (metabolic hormones measured by the 11-oxysteroids, androgens evaluated by the 17-ketosteroids). But in our patients the functional character of the hypercorticism is proved by its subsequent course. The clinical picture, which is rarely that of the complete Cushing syndrome, fades away slowly in later months. New levels of the 11-oxysteroids and 17-ketosteroids show the return to normal. Only hirsuties and striæ persist as an indelible trace of the endocrine flood.

The opinion that we already held about these obesities of transitory hypercorticism seen during puberty, has been strengthened by seeing cortisone reproduce the same syndromes. And so, besides the functional Cushing syndrome that we have described, a "pharmacodynamic" Cushing syndrome, also transitory, has been recognized.

Conclusion

Among the varied manifestations of puberty those of glandular hypersecretion are very common. These symptoms can be mistaken for a new growth, which is alarming. But spontaneous regression is the rule, at the cost of a few stigmata such as dysharmony of skeletal proportions after transitory hypersecretion of growth hormone, hirsuties, and striæ after adrenal hypercorticism.

The many mutual glandular reactions and the complexity of their nervous regulation accounts for the intricacy of the symptoms resulting from such hypersecretions and our sometimes arbitary delineation of the clinical picture.

Study of Variations of the Cœruloplasmin by an Easy Technique

By R. Turpin, H. Jerome and Mme H. Schmitt

Laboratoire de Thérapeutique, Faculté de Médecine de Paris

Most of the copper in serum is bound to a globulin. Abderhalden and Möller (1928) and later Yosikawa (1939) have established that the serum copper is not dialysable at physiological pH. Holmberg and Laurell (1947) by precipitating the serum proteins with half-saturated $(NH_4)_2\ SO_4$ and titrating the copper in this fraction, have observed that 90% of the total copper is bound to globulins. This copper does not react directly with sodium diethyldithiocarbamate, whilst copper added *in vitro* gives a direct reaction. This shows that the specific protein compound of copper is saturated, at least in most cases. Holmberg and Laurell (1948) have isolated and purified the cuproproteid. It is an alpha 2-globulin, called "cœruloplasmin" behaving as an oxidase with characteristic properties of a laccase. This cœruloplasmin may be an active form and not a transitional form. Indeed, Keiderling (1950) showed that the hypercupremia that follows administration to a dog of a large dose of copper, is entirely represented by a non-dialysable copper, but reacting directly with sodium diethyldithiocarbamate. With this exception, however, the serum copper as we have shown above, never reacts directly.

We have used a technique to estimate cœruloplasmin by measuring what we call globulin copper. Serum proteins are precipitated by ammonium sulphate at a saturation between 36 and 55%. The fraction so obtained contains 11% of total serum proteins. A paper electrophoretic study shows that the principal strip is located at the same level as alpha 2-globulins and represents 8% of the proteins, the remaining part being constituted by fractions of lower migration speed. Copper is titrated in the precipitate and compared with total copper in the serum. This technique may be easily undertaken in any clinical laboratory. Precipitation must be brought about in fresh serum, indeed, we have noticed that, in time, copper is dissociated from its specific protein, even at normal pH.

The results we have observed with this technique may be classified under two heads:

(*a*) Total Copper and Globulinic Copper Increase Together

Cœruloplasmin has been isolated by Holmberg and Laurell (1948) from pregnant women's serum. Pregnancy involves, in fact, a hypercupremia proportional to the cuproproteid increase.

We have noticed that in rat and man, a synthetic œstrogen, diethylstilbœstrol, heightens the cupremia. This hypercupremia is also due to an increase of globulinic copper: before treatment the total Cu = 83 microgrammes %, globulin Cu = 76 microgrammes % = 91·5% of total Cu; after diethylstilbœstrol total Cu = 145 microgrammes %, globulin Cu = 122 microgrammes % = 84% of total Cu.

The same phenomenon occurs in infections and anæmias.

(*b*) Total Copper and Globulinic Copper are Dissociated

Scheinberg and Gitlin (1952) either by a spectrophotometric, or by an "immunochemical" method have shown in hepatolenticular degeneration, the occurrence of a cœruloplasmin decrease. We have confirmed this fact by our technique and observed that the usual hypercupremia is contrasted by a decrease of globulin copper: total Cu = 155 microgrammes%; globulin Cu = 46 microgrammes% = 29·7% of total Cu.

On the other hand, during a systematic study of 25 parents, siblings and relatives of children dying with hepatolenticular degeneration, we have found 6 low percentages, between 50 and 61%

of globulin Cu to total Cu; and this in subjects free from any neurological symptoms. This unusual finding concerns three generations of the same family.

It is probable that this lack of cœruloplasmin, a cuproproteid which seems in some way connected with an enzymatic need of the organism, may be the underlying fault in hepatolenticular degeneration.

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The Genetics of Pyloric Stenosis

By MAURICE LAMY, Mme CL. POGNAN and P. MAROTEAU

UP to the present time, there has been no agreement concerning the ætiology of congenital pyloric stenosis, although some very important work has been done—mostly by British geneticists—on the part played by heredity and environment.

Several years ago, my co-workers and I began to study the genetics of pyloric stenosis. We decided to investigate only those cases in which the diagnosis had been proved correct by a surgeon at operation. We succeeded in collecting 504 children who had been operated on since 1925 either at the Hôpital des Enfants Malades or in one of several hospitals for sick children in Paris. By contrast, in order to establish a comparison, we studied 504 children of the same age, taken at random, and thus a non-selected sample of the whole population.

Pyloric stenosis is said to be much more frequent in boys and in first-born babies, and is reported to have a low familial incidence. Making a study of environmental, pre-natal influences, we first calculated the importance of maternal age and birth rank.

Concerning the maternal age, we found an average of 26·41 years (standard deviation $\pm$ 0·25).

In the control group, the mean was 25·90 (standard deviation $\pm$ 0·25). So, there is no significant difference between the two groups.

252 babies with pyloric stenosis were first-born babies, that very high proportion (50%) seems to support the view that primogeniture is a very significant ætiological factor. In fact, the proportion of first-born in the general population depends upon the mean size of the family in the community and is not easy to estimate. The French demographic institute was unable to give us any reliable information on that point. But, in our control group the percentage of first-born babies was, in fact, somewhat higher, 52·57% instead of 50%. There is, therefore, no significant difference between the two series. According to our inquiry, then, neither maternal age nor birth rank takes a part in the ætiology of pyloric stenosis.

Making a study of our 504 children we were fortunate to come across 8 pairs of twins. Three of these couples were monozygotic and in every one of these 3 cases both babies have been affected. Five were dizygotic twins and in no case were the two babies affected. That difference between MZ and DZ twins supports the view that genetic factors are very important.

Concerning the sex-ratio, we found a proportion of males to females of about 5 to 1. The percentage of boys was 83·49% and of girls 16·51%. The parents of the patients had never had pyloric stenosis, except in one single case. Concerning the sibs: in 17 families we found 2 cases of pyloric stenosis; in one family there were 3 cases and in another all the 4 children of the family had been operated upon for pyloric stenosis.

We recorded 9 consanguineous marriages among the parents of the propositi. They were first-cousin marriages.

According to the demographic institute the consanguinity rate in France is very near 1% (0·92). So, by mere chance we could have recorded 5 consanguineous unions. Therefore, the rate of consanguinity may be slightly increased but the difference is not significant. The χ^2 is 3·23 with one degree of freedom.

SUMMARY

From this study we may draw the conclusion that such environmental factors as maternal age and birth rank do not play any important part in the ætiology. The genic constitution has the greatest importance, as is proved by the comparison of twins. The disease is certainly not due to a single autosomal dominant gene, as both parents of an affected child are always normal. It cannot be due either to a sex-linked recessive gene; too many females are affected. Moreover, in the case of an affected female, the father should also be affected, but he is not.

The hypothesis of a recessive autosomal gene is the most likely. That is also Cockayne's and Pursey's opinion. The fact that the consanguinity rate is low is not surprising. We know that when a recessive disease is a rather frequent one, the consanguinity rate amongst parents does not rise significantly. According to McKeown and Brian McMahon the frequency of the disease is 3 per thousand which is a rather high figure.

Of course, in the case of a recessive autosomal disease, the incidence among sibs should be higher and there is no reason for the disease to be more frequent in males.

So we must admit firstly that the "pénétrance" of the gene is a rather low one, and secondly that genetic factors, some of them probably sex-linked, inhibit the "pénétrance," i.e., the manifestation of the recessive gene which is responsible for the disease.

[*May* 22, 1953]

THE following cases were shown:

Identical Twins with Pseudo-hermaphroditism.—Dr. S. WOLFF (for Dr. SIMON YUDKIN).

Adrenogenital Syndrome Treated with Cortisone.—Dr. B. GANS.

Bilateral Ureteric Calculi.—Dr. R. J. K. BROWN (for Dr. M. J. WILMERS).

Juvenile Myxœdema.—Dr. D. G. VULLIAMY (for Dr. P. R. EVANS).

Melorheostosis (X-rays only).—Dr. M. C. JOSEPH (for Dr. P. R. EVANS).

Non-osteogenic Fibroma of Bone.—Mr. R. C. FARROW (for Mr. D. LEVI).

Familial Macrocephaly.—Dr. R. C. ROXBURGH (for Dr. C. F. HARRIS).

[*June* 20, 1953]

MEETING HELD AT ALDER HEY CHILDREN'S HOSPITAL, LIVERPOOL

Renal Impairment, Hypertension and Encephalomalacia in an Infant Surviving Severe Intra-uterine Anoxia

By OLIVE SHARPE, M.B., Ch.B., D.C.H.
Pædiatric Registrar, Mill Road Maternity Hospital, Liverpool

and EDWARD G. HALL, M.B., B.Sc.
Consultant Pathologist, Alder Hey Children's Hospital, Liverpool

Dr. Olive Sharpe: A 28-year-old woman attended Mill Road antenatal clinic when she was 22 weeks pregnant. She had had two normal pregnancies previously each of which resulted in the birth of a normal baby at full term. She had not been anæmic during either of these pregnancies.

Nothing abnormal was found in her third pregnancy apart from anæmia. Her blood was Rh positive and the Kahn reaction was negative. At the 22nd week of her pregnancy her hæmoglobin was 10·4 grammes% but by the 34th week it had fallen to 8·3 grammes%. It was decided to treat the anæmia with Ferrivenin so as to effect a rapid rise in hæmoglobin. A test dose of 50 mg. Ferrivenin was given and there was no reaction. An intravenous drip of 1 gramme of Ferrivenin in 1 litre of 5% dextrose in water was set up. Six hours later, when she had had 850 mg. of Ferrivenin, she vomited and complained of severe abdominal pain and pain in the lumbar region. Twenty minutes later she became pulseless and there was blotchy cyanosis of her skin. The systolic blood pressure was 6[illegible] mm.Hg, the diastolic pressure could not be recorded. Her heart-rate (by auscultation) was 14[illegible]/minute. The fœtal heart-rate was 80/minute. The mother was given oxygen and 30 mg. Methedrine intravenously. The fœtal heart-rate remained at 80/minute for the next forty minutes and then was inaudible. It remained inaudible until one and a half hours later when the rate was 18[illegible]/minute and this rapid rate continued for the next six hours after which it dropped to 120/minute and it remained at this rate until delivery.

The mother's condition gradually improved after the Methedrine was given and her condition remained satisfactory and four days later she was delivered normally of a female child weighing 5 lb. 12 oz.

The baby's condition at birth was poor; there was gross generalized œdema, pallor, but no cyanosis. There was no detectable ascites, no pleural effusion and no enlargement of the liver or spleen. For the first two days of life the heart-rate was slow and the temperature subnormal and there was evidence of atelectasis. Oxygen was given, and penicillin and streptomycin were given prophylactically. After two days the temperature and heart-rate were normal and the lungs were well expanded. The œdema, however, did not disappear completely until eleven days after birth.

The baby was lethargic for the first two weeks of life but thereafter she took feeds well and began to gain weight. The skull, however, which appeared normal at birth did not increase in size, overlapping of the skull bones persisted and the child began to present a microcephalic appearance.

In the second month of life the child had recurrent periods of pyrexia for which no adequate cause could be found. She did not seem at all ill during these periods, she continued to feed well and to gain weight. Penicillin and streptomycin and later Chloromycetin were given but they failed to influence the course of the pyrexia which did not appear to be due to infection. At this time the child began to lie in a position of opisthotonos and uttered a whining cry. There was no neck stiffness and Kernig's sign was negative. She failed to show any mental development from birth. The blood pressure was not recorded until the child was 2 months old when the systolic pressure was raised to 174 mm.Hg and the diastolic to 80 mm.Hg. The blood pressure remained at this level throughout the rest of the child's life.

The baby was allowed home when she was 3 months old but her condition never improved. She was last seen at Out-Patients three days before her death which occurred when she was 4 months old.

Investigations on baby.—Blood W.R. negative. Coomb's test negative. Toxoplasmosis tests on the blood of the mother and child negative. X-ray skull: no evidence of intracranial calcification. Repeated X-rays of the chest and abdomen were normal. Full blood count was normal. Blood urea on second day of life 30 mg.% Blood urea at one month 118 mg.% and remained at this level until death. Blood sodium and chlorides were estimated several times and were within the normal range until three days before death when they reached the upper limit of normality. Serum proteins were at the lower limit of the normal range on the second day of life, but thereafter were normal.

Urine: In one specimen only a few leucocytes were seen but culture was sterile.

An intramuscular pyelogram showed excretion from the left kidney but the renal pelvis on the right side was not visualized.

Summary

The child at birth had gross and generalized œdema which cleared after eleven days.

Microcephaly developed after birth, with renal impairment and hypertension.

There was recurrent unexplained pyrexia from the second month after birth.

During the child's life it was difficult to link up these four phenomena. First, we considered that the baby's condition might be unrelated to the extreme degree of fœtal anoxia which was known to occur, but we were unable then to produce a satisfactory explanation on any one hypothesis. Second, we considered whether the changes produced might be due to the toxic effect of the iron itself. The work of Pommerenke and his colleagues (1942), using preparations of radioactive iron, indicates that iron crosses the placenta into the fœtal circulation. The experimental work of Nissim (1953) with animals has shown that if a dose of 45 mg. per kg. body weight is exceeded, intravascular precipitation of the Ferrivenin occurs and these precipitates cause pulmonary and systemic embolic phenomena. The dose in this case did not exceed the threshold level. It seemed more likely that the Ferrivenin was only important in that its administration produced a reaction which led to prolonged and severe fœtal anoxia. Circumstances in which the fœtal heart is inaudible for one and a half hours without intra-uterine death occurring must be very uncommon. The profound anoxia could explain the gross œdema which was present at birth, since, when water, electrolytes, and other constituents are lost from the fœtal plasma through damaged fœtal capillaries, they are replaced in the fœtal blood from the relatively great reserves in the maternal blood and tissues, so that gross œdema may occur and the plasma of the infant may reflect this imperfectly (Morison, 1952). Severe anoxic damage to the brain could explain the microcephaly. The renal impairment, hypertension and recurrent pyrexia were difficult to interpret, but again it was postulated that the renal impairment might be the result of changes in the renal tissue following profound anoxia.

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Dr. E. G. Hall: At autopsy there were abnormal features in three organs. A moderate degree of concentric hypertrophy of the left ventricle, without other gross or microscopic changes in the heart or great vessels, substantiated the clinical observation of hypertension of some duration.

There was no evidence of a primary disorder of skull development to account for the microcephaly, but the brain, though presenting a normal convolutional pattern and of normal size in relation to the skull, showed almost complete replacement of the white matter of the hemispheres by flaccid cysts of varying size (Fig. 1). The walls of the cysts were granular, and contained yellow-brown areas of iron pigmentation. Vascular trabeculæ traversed many of the spaces. The basal nuclei contained patchy areas of necrosis, but cerebellum and cord were macroscopically normal. The ventricles were slightly dilated and their walls of normal appearance. There were no communications between the cysts and the ventricular lumina or the subarachnoid space. The histological changes were those of necrosis, phagocytosis and separative gliosis only.

There was no macroscopic abnormality of the kidneys, but on section there were striking changes in the medulla, presenting as a regular pattern of bands of fibrous tissue, enclosing minute atrophic tubules, running centrally from the cortico-medullary junction, to fuse together into a uniform atrophic fibrosis of the inner medulla (Fig. 2). Fragments of necrotic tubules were seen, and there were

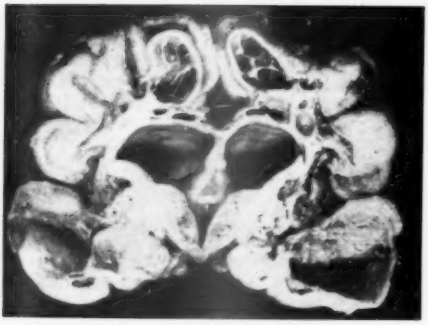

FIG. 1.—Transverse section of brain showing widespread cyst formation.

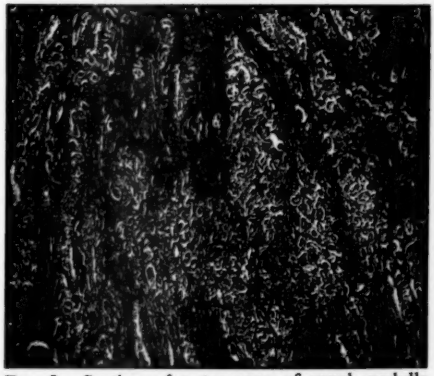

FIG. 2.—Section of outer zone of renal medulla showing fibrous bands containing atrophic tubules.

hæmosiderin deposits scattered fairly evenly throughout the fibrous tissue. In the cortex the peripheral glomeruli were healthy, but the majority of the juxtamedullary glomeruli showed fibrotic changes similar to those seen not infrequently in a few glomeruli in the healthy kidney of the young infant, and described by Friedman, Grayzel and Lederer as "Congenital Glomerulosclerosis". There was no evidence of a congenital malformation of the kidneys, nor of a chronic pyelonephritis.

The pathological findings supported the clinical hypothesis of normal fœtal development until shortly before delivery, and we were unable to find any evidence of ætiological factors unrelated to the events immediately preceding birth.

We suggest that the hypothesis of severe fœtal anoxia best explains the pathological as well as the clinical features of this case. The central type of porencephaly may well have developed in a similar fashion to that described by Schwartz in the brains of severely asphyxiated infants. Though the pathogenesis of the renal lesion is obscure, the production of renal atrophy by short periods of arterial occlusion, as in the experiments of Koletsky and Dillon, indicates that anoxia alone might be the responsible factor, and Badenoch and Darmady have shown that one of the early effects of renal arterial occlusion in rabbits is damage to the loops of Henle in the medulla.

We have presented this case to point out that high dosage of an intravenous iron preparation may in pregnancy cause severe symptoms in the mother and secondary injury to the fœtus, and to suggest that severe fœtal anoxia may be responsible for the unusual clinical and pathological features of this case.

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Some Observations on the Use of Fructose and Invert Sugar in Infants

By R. McLaren Todd, M.A., M.D., M.R.C.P., D.C.H.
Senior Lecturer in Child Health, University of Liverpool

During the past decade intravenous infusions have been used frequently to restore the fluid and electrolyte balance of sick infants and children, and to supply carbohydrate and amino-acids when oral feeding was contra-indicated. One of the commonest solutions used for intravenous infusion is 5% glucose, and this has a calorie value of approximately 200 calories per litre. In some patients a high calorie intake may be desirable; but if more concentrated glucose solutions are given intravenously there is a risk of venous thrombosis because the sugar solutions are hypertonic; and also, because the blood sugar may rise above the renal threshold level, there may be a loss of glucose in the urine. If, on the other hand, the calorie intake is raised by increasing the volume of the infusion there is a risk of overloading the circulation and causing cardiac failure and generalized œdema. Alternative sugar solutions with a higher calorie value have been used and during the two world wars, chiefly because glucose was scarce, invert sugar was sometimes substituted. Invert sugar is obtained from cane sugar by treating it with dilute acid or with the enzyme invertase. The resulting solution contains equal amounts of glucose and fructose, and unlike cane sugar which rotates the plane of polarized light to the right, invert sugar is lævo-rotatory, i.e. the rotation has been inverted.

During the past three years American workers (Weinstein 1950 and 1951, Weinstein and Roe 1952, Miller *et al.* 1952) have studied the metabolism of fructose and invert sugar in animals, in healthy adults, and in adults suffering from diabetes mellitus. These workers gave 10% and 15% invert sugar solutions intravenously and found that this sugar was utilized rapidly, that the blood sugar levels did not exceed the renal threshold, that little if any sugar was excreted in the urine and that the solution did not cause venous thrombosis.

Present Investigations

Because of the possible value of invert sugar in some pædiatric disorders, I have undertaken similar investigations, during the past six months, both in normal healthy infants and in infants suffering from gastro-enteritis. The preliminary investigations were made on infants between 3 and 6 months of age who had recovered from the illnesses for which they were originally admitted to hospital. Fructose and invert sugar* solutions of different concentrations were administered to these infants either intravenously or by mouth. The levels of blood sugar were followed for periods up to eight hours and compared with the levels after giving equivalent concentrations of glucose.

The detailed arrangements of the investigations were as follows:

A. *Intravenous*

An infant who has received a normal diet for five days was given the last feed at 10 p.m. on the night before the test, and boiled water at 6 a.m. on the day of the test.

A *scalp vein infusion* of 20 c.c. fluid per pound was given over a period of six hours.

Blood sugar levels were taken at 9.30 a.m., 11.30 a.m. and hourly thereafter until 5.30 p.m.

Urine was collected and tested for sugar at 9.30 a.m. and at two-hourly intervals thereafter.

B. *Oral*

The preparation of the infant was the same as for the intravenous investigations.

Oral fluid was given by bottle at 9.30 a.m. in a volume of 20 c.c. per pound in fifteen to twenty minutes.

Blood sugar levels were taken at 9.30 a.m., 10 a.m., 10.30 a.m., 11.30 a.m., 12.30 p.m., and 1.30 p.m.

Urine was collected and tested for sugar at 9.30 a.m. and at two-hourly intervals thereafter.

The seven solutions used in both intravenous and oral investigations were as follows:

1. N/5 saline and 5% glucose
2. „ „ „ 5% fructose
3. „ „ „ 7·5% glucose
4. „ „ „ 7·5% fructose
5. N/5 saline and 10% glucose
6. „ „ „ 10% fructose
7. „ „ „ 10% invert sugar ("invose")*

*The preparation of invert sugar used was "Invose" kindly supplied by Herts Pharmaceuticals Ltd.

Figs. 1 and 2 record the blood sugar levels after giving solutions of glucose, fructose and invert sugar in an infant of 5 months of age. Other infants were investigated and similar readings obtained.

After these preliminary investigations it was decided to use invert sugar in the treatment of infants suffering from gastro-enteritis. These infants were chosen because the disease is fairly common in young babies, and it is a condition for which glucose solution is given either orally or intravenously.

A standard regime for the treatment of this condition is in use at Alder Hey Children's Hospital and this regime was followed except that in alternate cases 10% invert sugar was substituted for 5% glucose solution. In these infants the electrolytes (such as potassium) given were similar, and the regrading of milk feeds was also similar.

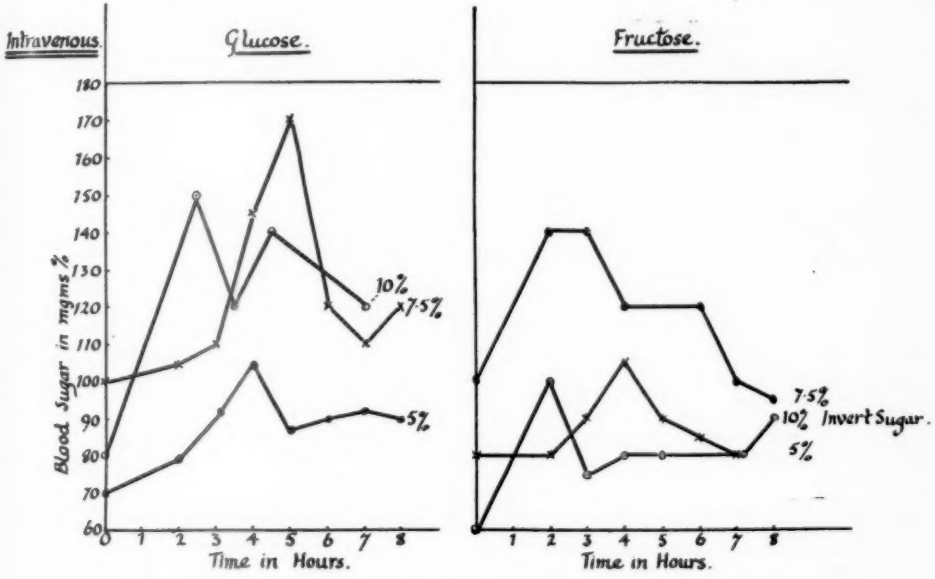

FIG. 1.

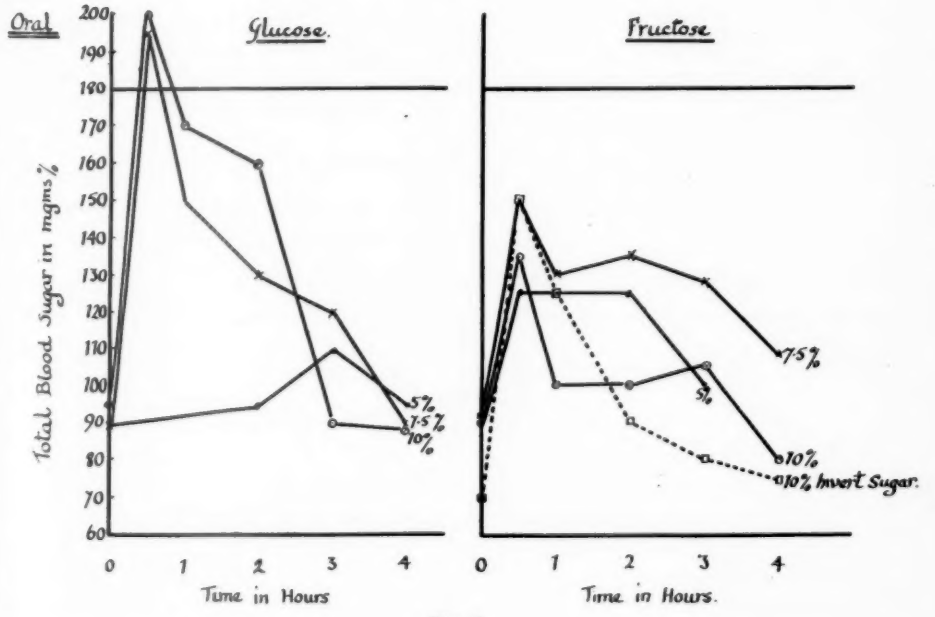

FIG. 2

The results of treatment in 34 infants with gastro-enteritis are shown in Table I. "Mild" cases were given oral fluids only. "Severe" cases required intravenous therapy initially.

TABLE I

Gastro-enteritis 34 patients		Number of patients	Diarrhœa in days Before admission	Diarrhœa in days After admission	Days to clinical recovery
Glucose	Mild	9	5·4	6·6	8·3
	Severe	9	5·0	8·1	10·1
Invert sugar	Mild	7	3·1	9·8	11·1
	Severe	9	4·0	6·6	9·4

Progress appeared to be equally satisfactory in the two groups: no prolongation of diarrhœa resulted from the 10% sugar solution; no venous thromboses were encountered; one or two infants appeared to dislike "invose" but this anorexia may well have been the result of the gastro-enteritis.

COMMENTS

These investigations have shown that invert sugar provides a satisfactory alternative sugar solution for intravenous and oral use in infants. The blood-sugar readings after giving 10% invert sugar and 10% fructose do not reach the renal threshold level and the levels of blood sugar are lower than those found after giving equivalent strengths of glucose. These findings are in accord with those of Weinstein (1950, 1951) who showed that fructose is more readily phosphorylated and used more rapidly than glucose, and that when glucose and fructose are given together glucose is removed more rapidly from the blood stream than when it is given alone, i.e. fructose has a catalytic effect on glucose metabolism.

In some patients it is advantageous to give a high calorie intake intravenously without giving an extra fluid volume. Although in our investigations into the value of invert sugar infants suffering from gastro-enteritis were studied, it is likely that invert sugar will prove to be of greater value in infants and children suffering from certain surgical conditions.

In some of these patients in whom oral fluids are contra-indicated and intravenous therapy has to be employed for several days, it will be advantageous to use a sugar preparation which will increase the calorie intake by up to 100% without increasing the volume of fluid infused.

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[Dr. S. E. Keidan's paper on Elephantiasis Nostras will appear in *Lancet*.

Mr. P. P. Rickham's paper on Annular Pancreas in the Newborn will appear in *Arch. Dis. Childh.*]

Section of Endocrinology

President—S. LEONARD SIMPSON, M.A., M.D., F.R.C.P.

[*January* 28, 1953]

DISCUSSION ON PHÆOCHROMOCYTOMA

(see *British Heart Journal*, 1953, **15**, 241)

[*February* 25, 1953]

JOINT MEETING WITH THE SOCIETY FOR ENDOCRINOLOGY

SYMPOSIUM ON THYROID GLAND

The following papers were read:

Introduction.—Sir CHARLES HARINGTON.

Biosynthesis of the Thyroid Hormone and Biochemical Aspects of its Secretion.—J. ROCHE, S. LISSITSKY, and R. MICHEL.

Recent Work on the Nature of the Thyroid Hormone.—Mrs. R. V. PITT RIVERS.

The Significance of Lymphadenoid Nodules in the Thyroid Gland.—RAYMOND GREENE.

Some Observations on Thyroid Histology and Reproductive Efficiency in Cattle.—S. L. HIGNETT.

Anti-thyroxine Compounds.—Professor N. F. MACLAGAN.

The Natural History of Graves' Disease as Revealed by Treatment with Anti-thyroid Drugs.—W. R. TROTTER.

Thyroid Activity in the Rabbit.—Professor G. W. HARRIS, C. VON EULER, J. BROWN-GRANT, and S. REICHLIN.

Response of the Thyroid to Thyrotrophic Hormone.—A. STUART MASON.

The Usefulness of Radioiodine in Clinical Diagnosis.—RUSSELL FRASER.

The Diagnostic Value of Serum Protein-bound Iodine Estimation.—R. R. DE MOWBRAY, and A. TICKNER.

Concluding Remarks.—S. LEONARD SIMPSON.

(For report of the meeting see *Memoirs of the Society for Endocrinology*, The Thyroid Gland, No. 1, July 1953. Bath).

[*March* 25, 1953]

The following cases were shown:

Simmonds' Disease with Diabetes Mellitus.— Dr. OLIVER GARROD (for Dr. RUSSELL FRASER).

Gynæcomastia Treated with Plastic Surgery.— Mr. PATRICK CLARKSON.

The Effect of a Long-acting Preparation of ACTH in Panhypopituitarism.—Dr. A. A. G. LEWIS.

Addison's Disease and Diabetes Mellitus Treated by Cortisone.—Dr. S. LEONARD SIMPSON.

Dwarfism and Infantilism with Polycythæmia—Case for Diagnosis.—Dr. M. HARINGTON (for Dr. JOHN F. STOKES).

[*April* 22, 1953]

Cushing's Syndrome with Special Reference to Bilateral Adrenalectomy

By RANDALL G. SPRAGUE, M.D.

Section of Medicine, Mayo Clinic and Mayo Foundation[1], *Rochester, Minnesota*

THE principal theme of my discussion will be subtotal or total bilateral adrenalectomy as a method of treatment of Cushing's syndrome. However, I would first like to present certain other aspects of the problem of Cushing's syndrome which provided background for our decision to embark on this somewhat radical form of treatment of the condition at the Mayo Clinic in the summer of 1945[2].

Definition.—At the outset it is important that the term "Cushing's syndrome" be reserved for patients who present most or all of the physical and laboratory features described by Cushing and by subsequent students of the condition (Table I). Although the majority of patients have hirsutism

TABLE I.—CUSHING'S SYNDROME

Symptoms and Signs	
Obesity of trunk, face and neck	Thin skin
Cervicodorsal hump	Cutaneous striæ
Weakness	Ecchymosis
Polyuria	Acne
Amenorrhœa or impotence	Hirsutism
Psychic changes	Osteoporosis
Muscle wasting	Hypertension
	Œdema
Laboratory Findings	
Impaired glucose tolerance, or frank diabetes	Alkaline urine
Hypopotassæmia	Lymphopenia
Hypernatræmia	Eosinopenia
Hypochloræmia	Polycythæmia
High plasma bicarbonate (alkalosis)	Increased excretion of corticosteroids in urine

and acne of some degree other evidences of virilization are lacking. While not every patient presents all of the features outlined in Table I, the term should not be applied to obese women with hirsutism and menstrual abnormalities, who do not have unequivocal evidence of adrenal cortical hyperfunction.

Endocrine pathology.—Cushing's syndrome has been reported in different cases to be associated with a wide variety of endocrine lesions, including basophilic tumour of the anterior pituitary, Crooke's hyaline changes in the basophilic cells of the anterior pituitary, parathyroid tumour, thymoma, adrenal cortical hyperplasia or tumour and adrenal-like tumour of the ovary. Nevertheless, there is overwhelming evidence that the symptoms in all cases result from hyperfunction of the adrenal cortex. The most recent evidence of this is the production of virtually all the signs and symptoms of the syndrome by administration of corticotropin or cortisone. Indeed, the capacity of exogenous cortisone to induce the syndrome suggests that the spontaneously occurring syndrome may be largely due to overproduction of a single steroid of this type.

It is frequently assumed that Cushing's syndrome in the absence of an adrenal cortical tumour is a consequence of overproduction of corticotropin by basophilic cells of the anterior pituitary. We have, however, rarely been able to demonstrate corticotropic activity in the blood or urine of patients with Cushing's syndrome. Experience at the Mayo Clinic with the assay of corticotropin in the blood of patients with Cushing's syndrome and other conditions has recently been reviewed by Paris and associates (1953).

Thus, on the basis of established knowledge of the endocrine defect in Cushing's syndrome there seems to be a sounder rationale for treatment directed to the adrenal cortices than for any other form of therapy.

Prognosis.—The syndrome is generally regarded as a somewhat serious condition, but until recently there have been few actual data on survival. Gorsuch (1949), in a review of a series of cases from the

[1]The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

[2]The care and study of these patients has been a collaborative venture involving all of my colleagues in the Sections of Metabolism and three members of the surgical staff of the Mayo Clinic, namely, Dr. O. T. Clagett, Dr. J. T. Priestley and Dr. Waltman Walters. Studies of urinary steroids were done in the laboratory of Dr. H. L. Mason and other chemical determinations were done in the laboratory of Dr. M. H. Power. Assays of corticotropic activity in blood were made in the laboratory of Dr. A. Albert. Dr. E. J. Kepler, whose interest in Cushing's syndrome provided the early impetus for treatment of the condition by adrenalectomy, played a prominent part in these studies up to the time of his death in 1947.

literature and from Mayo Clinic necropsy material, found that the survival after diagnosis varied from three days to thirteen years. In a recently published study Plotz, Knowlton and Ragan (1952) found that 17 of 32 patients with the syndrome were dead within five years of the onset of symptoms. A study of survival has been compiled recently on 54 patients at the Mayo Clinic on whom surgical exploration had failed to disclose an adrenal cortical tumour and on whom adrenal resection was not performed. All 54 patients were traced (Table II). It is apparent that the three-year and five-year survival rates are significantly lower than would be anticipated in the general population.

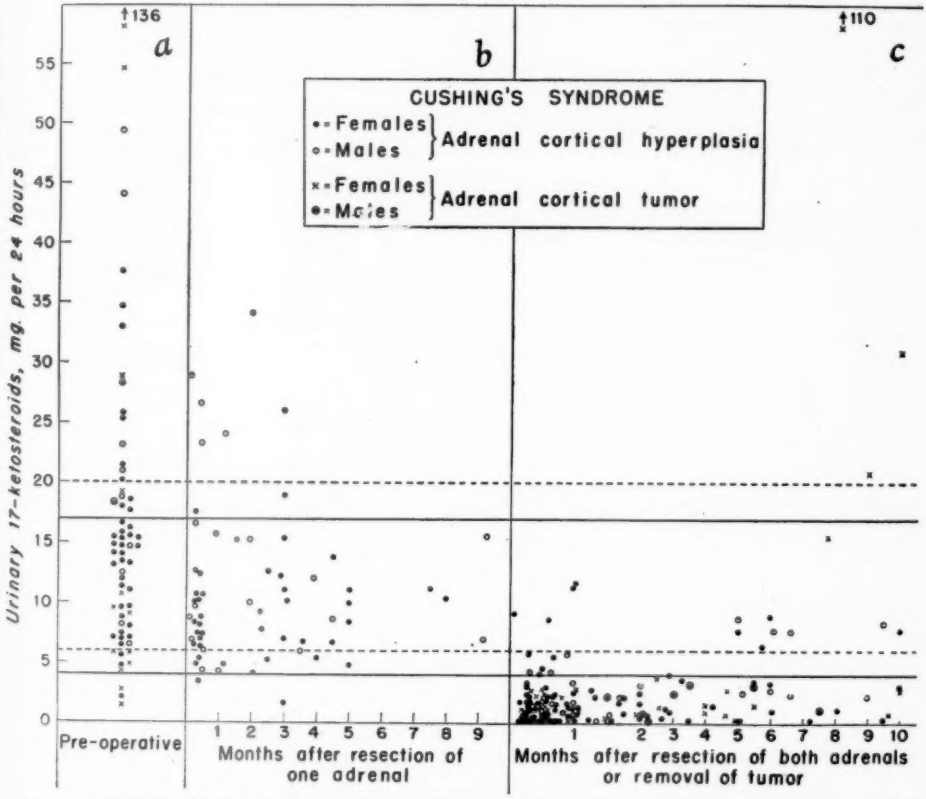

FIG. 1.—Urinary 17-ketosteroids in patients with Cushing's syndrome associated with adrenal cortical hyperplasia or adrenal cortical tumour. *a*, Pre-operative values in 50 patients with hyperplasia and 14 patients with tumour. *b*, Values at varying intervals after resection of one adrenal gland in 36 patients with hyperplasia. *c*, Values at varying intervals after completion of bilateral adrenal resection in 45 patients with hyperplasia and after removal of tumour in 14 other patients. The range of normal values for men lies between the horizontal broken lines and that for women between the horizontal solid lines. [Reprinted from Sprague, R. G., Kvale, W. F., and Priestley, J. T.: Management of Certain Hyperfunctioning Lesions of the Adrenal Cortex and Medulla (1953) *J. Amer. med. Ass.*, **151**, 629.]

The morbidity caused by the condition also provides some justification for a radical approach to therapy. Cardiovascular disease, renal disease, susceptibility to infection, disabling osteoporosis, muscular weakness, physical disfigurement and psychic changes all contribute to the overall morbidity of the syndrome.

The importance of surgical exploration of the adrenal glands.—Identical clinical syndromes may be produced by a functioning tumour of the adrenal cortex and by adrenal cortical hyperplasia. Although in an occasional case the presence of a tumour of the adrenal cortex may be detected by physical examination or by various roentgenographic methods, there are no clinical or laboratory findings known to-day which will permit the accurate differentiation in all cases between tumour and hyperplasia. Radiography probably cannot be relied on in all cases to demonstrate the presence or absence

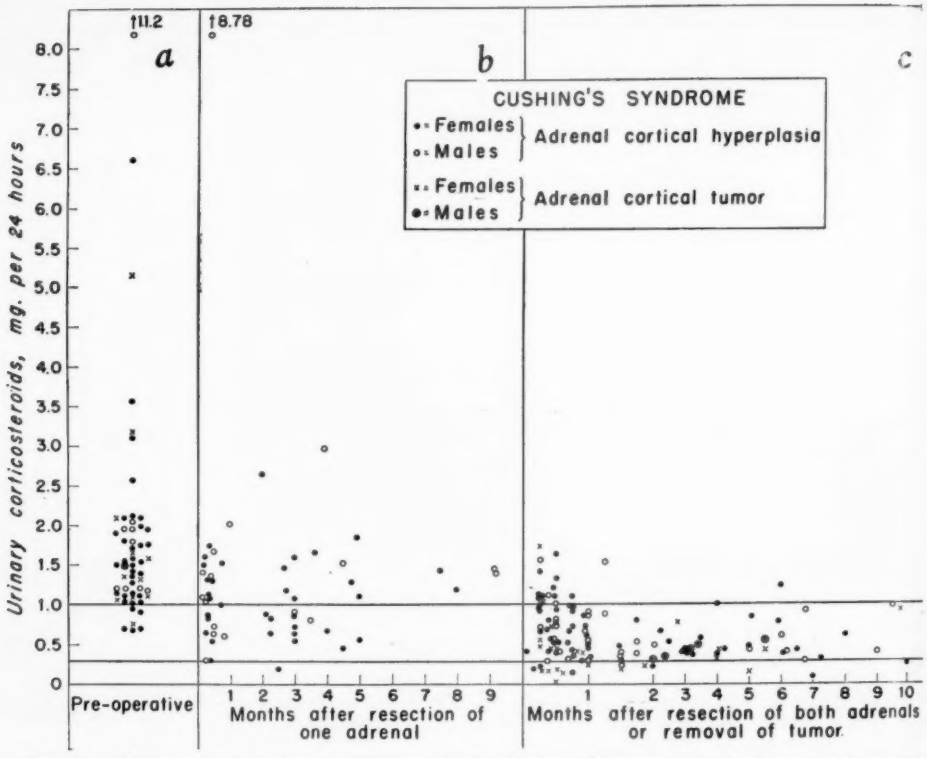

FIG. 2.—Urinary corticosteroids in patients with Cushing's syndrome associated with adrenal cortical hyperplasia or adrenal cortical tumour. *a*, Pre-operative values in 44 patients with hyperplasia and 12 patients with tumour. *b*, Values at varying intervals after resection of one adrenal gland in 31 patients with hyperplasia. *c*, Values at varying intervals after completion of bilateral adrenal resection in 41 patients with hyperplasia and after removal of tumour in 12 other patients. The range of normal values for men and women lies between the horizontal solid lines. [Reprinted from Sprague, R. G., Kvale, W. F., and Priestley, J. T.: Management of Certain Hyperfunctioning Lesions of the Adrenal Cortex and Medulla (1953) *J. Amer. med. Ass.*, **151**, 629.]

TABLE II.—CUSHING'S SYNDROME: 3- AND 5-YEAR SURVIVAL RATES

Period after diagnosis, years	Total patients*	Lived beyond indicated period		Normal survival rate %†
		No.	Survival rate %	
3	46	31	67·4	98·7
5	43	25	58·1	97·9

*All patients were traced as of January 1, 1953. Average age of patients at time of diagnosis was 33 years.

Of the 54 patients, 7 patients who died in the hospital after operation plus 1 who died one day after dismissal are excluded in the calculation of the survival rates.

†Estimated survival rates in a population of same age and sex constitution.

TABLE III.—WEIGHTS OF TUMOURS IN 20 CASES OF CUSHING'S SYNDROME ASSOCIATED WITH ADRENAL CORTICAL TUMOUR*

Weight of tumour, grammes	Cases
5·4–20	10
21–40	5
More than 40	5

*Smallest tumour weighed 5·4 grammes; largest tumour, 600 grammes.

of a tumour because of the small size of the tumour in some cases. Weights of the tumours in 20 cases of Cushing's syndrome associated with adrenal cortical tumour are given in Table III. One tumour weighed only 5·4 grammes, and the tumours in half of the cases weighed 20 grammes or less. Neither can estimation of values of 17-ketosteroids and corticosteroids be relied on for aid in diagnosis. In only a rare case does the finding of a high excretion of urinary 17-ketosteroids with a high percentage of beta-17-ketosteroids permit accurate diagnosis of tumour, usually malignant, in advance of surgical exploration. As Forbes and Albright (1951) have pointed out, the finding of a low excretion of 17-ketosteroids may suggest the presence of a benign tumour; however, in the majority of our cases of Cushing's syndrome due to tumour the values for 17-ketosteroids overlapped the values obtained in cases without tumour (Fig. 1, pre-operative values). Neither do the values for urinary corticosteroids (formaldehydogenic steroids) differ significantly in the cases with and without tumour (Fig. 2, pre-operative values).

Thus, we have concluded that the possible presence of a removable tumour of the adrenal cortex is, in itself, sufficient justification for surgical exploration of the adrenal glands in all cases of Cushing's syndrome in which the condition of the patient permits. If a tumour is found and removed, remission of the syndrome occurs (Fig. 3). In a series of cases without tumour subtotal or total adrenalectomy has been performed with results which will be described.

FIG. 3.—Cushing's syndrome associated with adrenal cortical tumour in a woman, aged 24. *a*, Before development of the syndrome. *b*, Before operation. *c*, Six months after removal of tumour which weighed 10·5 grammes. [Reprinted from Walters, W. and Sprague, R. G.: Hyperfunctioning Tumours of the Adrenal Cortex With Report of Eight Cases (1949) *Ann. Surg.*, **129**, 677.]

PRE-OPERATIVE AND POST-OPERATIVE USE OF CORTISONE

Adrenal cortical function is likely to be inadequate in the period immediately after operation, regardless of whether a tumour of the adrenal cortex is found and removed or subtotal or total resection of hyperplastic adrenal glands is performed. After removal of a tumour of one adrenal gland the patient is left for a time with an atrophic, hypofunctioning adrenal gland on the opposite side. After total adrenalectomy on one side and radical subtotal adrenalectomy on the other side, only a small remnant of hyperplastic adrenal tissue remains, the function of which is likely to be inadequate under the conditions of stress in the post-operative period.

Pre-operative preparation consists of intramuscular administration of 200 mg. of cortisone forty-eight and twenty-four hours before the operation and again on the morning of the operation. Post-operatively, cortisone is given intramuscularly for about six days, in a gradually decreasing dose. Since we adopted this method of pre-operative and post-operative treatment with cortisone, acute adrenal insufficiency of serious degree has occurred in only 1 of our cases during administration of cortisone and there have been only 2 hospital deaths in the 37 operated cases.

IDENTIFICATION AND SURGICAL TREATMENT OF THE CAUSATIVE ADRENAL LESION

If pre-operative preparation has been adequate, it is not essential that it be known prior to operation whether the syndrome is due to an adrenal cortical tumour or to adrenal cortical hyperplasia[1].

[1] The term "adrenal cortical hyperplasia" is used in a loose physiologic sense to designate hyperfunctioning adrenal glands that are not the site of a tumour. In our experience, such adrenal glands are of normal weight in some cases of frank Cushing's syndrome and definite cytologic evidence of hyperplasia may be lacking in routine sections. Multiple small adenomas may be present.

However, my surgical colleagues emphasize the importance of determining accurately during the operation the nature of the adrenal lesion. This can be accomplished in most cases by consideration of the appearance of the first adrenal gland exposed. A tumour is easily recognized and removed and nothing further is done. On the other hand, if there is a functioning tumour of the contralateral adrenal gland the first gland exposed will be atrophic. In this case the incision is closed after biopsy and the opposite adrenal gland is then exposed with a reasonable expectation of finding a tumour, which is then removed. With experience the surgeon can usually recognize an atrophic gland from its gross appearance. If there is a doubt regarding the gland first exposed, the opposite gland should be inspected before more than a small specimen is removed from the first gland. If neither a tumour nor an atrophic gland is found on the side first exposed, then subtotal (85 to 90% of total) resection of the gland is performed. The opposite adrenal gland is then exposed and totally removed.

In our experience hyperplasia is approximately five times as common as tumour as a cause of Cushing's syndrome. In our recent cases bilateral adrenalectomy has been performed in one stage in cases of hyperplasia; however, operation in two stages may be employed if bilateral simultaneous adrenal resection is considered inadvisable.

Subtotal or Total Adrenalectomy for Cushing's Syndrome in the Absence of Tumour of the Adrenal Cortex

The following remarks concern only those patients who have Cushing's syndrome in the absence of tumour. These constitute the majority of all patients.

In our opinion our first attempts to treat Cushing's syndrome by radical subtotal adrenalectomy in the summer of 1945 were justified by the lack of reliable medical treatment, the uncertain response to roentgen irradiation of the pituitary and the poor prognosis in many cases, if left untreated. It was reasoned that radical reduction of the mass of hyperfunctioning adrenal tissue, regardless of what the remote cause of the condition might be, should bring about remission of the signs and symptoms of the disease, much as subtotal thyroidectomy brings about a remission of Graves' disease. This was proved to be true (Fig. 4).

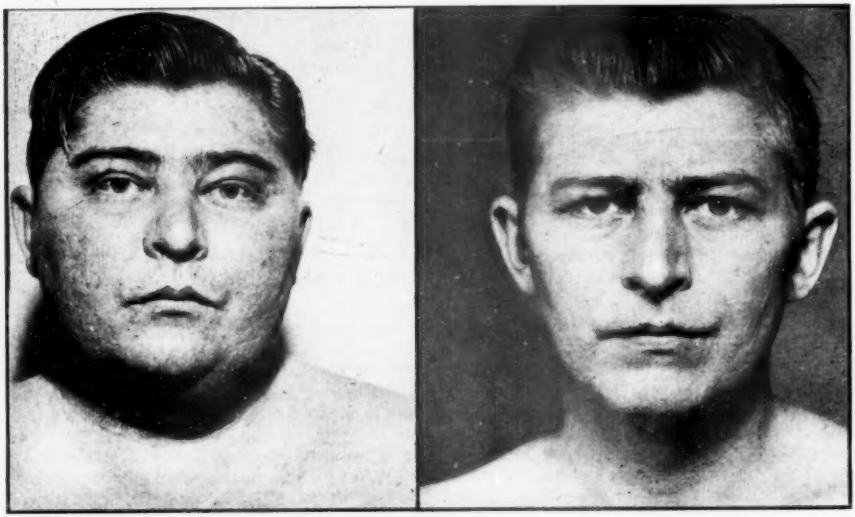

Fig. 4.—Cushing's syndrome associated with adrenal cortical hyperplasia in a man, aged 34. *a*, Before operation. *b*, Eight months after completion of subtotal adrenalectomy. The adrenal which was totally removed weighed 26·5 grammes. The patient also had roentgenologic evidence of a pituitary tumour.

Data are available concerning 58 cases of Cushing's syndrome in which radical subtotal or total resection of the adrenal glands was performed at the Mayo Clinic after exploration had failed to reveal an adrenal cortical tumour[1].

[1]The first 4 cases of this series have been described briefly by Kepler and associates (1948), the first 29 cases have been the subject of a preliminary report by Priestley and associates (1951), and recently the first 50 cases have been reported by Sprague, Kvale and Priestley (1953).

Clinical material.—43 of the patients were females and 15 were males. Their ages ranged from 13 to 60 years and averaged 34·6 years. All presented a combination of clinical and laboratory findings which warranted a diagnosis of Cushing's syndrome. In most the condition was moderately severe or severe, though the more recent cases are somewhat milder. Hypertension was present in all but 7 cases. Of 48 patients whose glucose tolerance was investigated, 39 had evidence of either frank or latent diabetes. The urinary excretion of 17-ketosteroids varied over a wide range but the excretion of corticosteroids (formaldehydogenic steroids), determined by a modification of the method of Corcoran and Page (1948), was higher than the maximal normal amount of 1 mg. per twenty-four hours in all but 5 cases.

Weights of totally removed glands.—The weights of 52 adrenal glands which were totally removed from 48 of the 58 patients are known. The weight of all but 5 was greater than 6 grammes, which is commonly considered normal. It is evident that marked adrenal enlargement is not a necessary accompaniment of Cushing's syndrome in the absence of tumour, for 17 of the glands weighed less than 7·5 grammes. The largest gland weighed 26·5 grammes and the smallest weighed 3·7 grammes. The average weight of the totally removed glands was 9·3 grammes.

Amount of gland removed.—When one gland was totally removed, the other was subtotally (85 to 90%) resected in all except 4 cases. In these 4 cases bilateral total adrenalectomy was performed. When subtotal adrenalectomy was performed, an effort was made to leave an adequate blood supply to the remaining remnant. We have come to believe that a high proportion, probably 90% or more, of the total amount of adrenal tissue must be removed to ensure consistent remission of the syndrome without appreciable hazard of recurrence. Experience to date suggests that to ensure a lasting remission the resection must be almost extensive enough to give rise to adrenal insufficiency.

Mortality (Table IV).—Among 54 patients treated by subtotal adrenalectomy there were 7 hospital deaths. Among 4 patients treated by total adrenalectomy there were no hospital deaths. 5 of the

TABLE IV.—RESULTS OF EXTENSIVE ADRENAL RESECTION IN 58 CASES OF CUSHING'S SYNDROME ASSOCIATED WITH ADRENAL CORTICAL HYPERPLASIA*

Results	Patients
Post-operative death	7
Died later	4
Living	
Now in remission*	46
Not in remission	1

*2 patients required re-operation because of incomplete remission. 3 patients required re-operation because of recurrence. 1 patient had roentgen therapy to the pituitary because of recurrence.

deaths occurred in the first 13 cases of the series. The use of cortisone for pre-operative and post-operative treatment was undoubtedly an important factor in decreasing hospital mortality in the later cases. Thus, among 21 patients who were operated on before cortisone was available and were treated with aqueous adrenal cortical extract there were 5 hospital deaths, whereas among 37 patients who were treated with cortisone there were but 2 hospital deaths.

Subsequently, there were 4 more deaths: 1 patient died at home two months after subtotal adrenalectomy, probably of adrenal insufficiency. Another patient committed suicide while in an apparently complete remission eighteen months after subtotal adrenalectomy. A third patient died of hypertensive and coronary heart disease four months after subtotal adrenalectomy. She had had Cushing's syndrome for a long time associated with severe vascular disease. The fourth death occurred four months after total adrenalectomy. The patient had had Cushing's disease for a long time associated with severe cardiovascular disease, thrombocytopenic purpura and Guillain-Barré syndrome.

47 of the patients in the series are alive at the time of writing.

Remissions and recurrences.—Where bilateral adrenalectomy was performed in two stages, no complete remissions of the signs and symptoms of the syndrome were observed after resection of only one hyperplastic adrenal gland. On the other hand, after completion of bilateral adrenalectomy, the signs and symptoms of the condition gradually regressed except that hypertension persisted in some cases and X-ray evidence of osteoporosis was slow to regress. Of the 47 patients who survived subtotal or total adrenalectomy all but one are in remission from Cushing's syndrome. Of those 47, 2 had another operation for removal of more adrenal tissue because of incomplete remissions following the initial subtotal adrenalectomy, and 3 others required re-operation because of recurrence of the syndrome after remissions lasting three, four and six years, respectively. Another patient experienced a complete remission after subtotal adrenalectomy but a fulminating recurrence developed eleven months later. A second complete remission followed roentgen irradiation of the pituitary. In all likelihood the second remission in this case was spontaneous rather than due to roentgen therapy as the dose employed was small and the treatment was never completed.

In the 46 now in remission, exclusive of the aforementioned patients who required re-operation because of recurrence, the time elapsed since operation varies from three months to eight years. In the subtotally adrenalectomized group additional recurrences can probably be anticipated with the passage of more time, since it must be presumed that the original stimulus to adrenal cortical hyperfunction may continue even after a remission has been induced by adrenalectomy.

Incidence of chronic adrenal insufficiency after operation.—23 of the 47 surviving patients are now receiving replacement therapy consisting of orally administered cortisone acetate alone or in conjunction with desoxycorticosterone acetate given buccally. Desoxycorticosterone acetate has been employed in addition to cortisone acetate in cases in which abnormalities of the plasma electrolytes persisted during treatment with cortisone alone. For the most part these patients have been maintained in good health. In some cases replacement therapy has been employed without positive knowledge that it was necessary. A few patients have been observed who initially required replacement therapy but eventually regained sufficient adrenal cortical function to permit stopping the treatment.

Delayed post-operative reaction.—Until early in 1951, it was our usual practice to discontinue replacement therapy after the early post-operative period because of concern about inhibition of the function of the adrenal remnant by administration of cortisone. Since then, however, replacement therapy has been employed in a high proportion of cases, partly because the trend toward more radical adrenal resections has increased the incidence of adrenal insufficiency and partly because it was discovered that administration of cortisone will avert or correct a peculiar post-operative reaction which began two to three weeks after adrenalectomy. This was characterized by weakness, depression, anorexia, abdominal pain, nausea, vomiting, muscular and articular symptoms, lymphocytosis and in some instances hypercalcæmia. It caused prolonged illness and disability, and terminated fatally in 2 cases. It was soon discovered that administration of cortisone would promptly relieve the symptoms. The reaction seemed to be related to the drastic reduction of adrenal cortical function from a supernormal to a subnormal level in patients who were conditioned to excess amounts of adrenal hormones; its precise mechanism, however, was never clear.

Changes Following Adrenalectomy

(1) *Changes in blood pressure.*—The blood pressure was significantly reduced after adrenalectomy in most cases (Table V). If hypertension be defined as a systolic pressure over 150 mm. of mercury or a diastolic pressure in excess of 90 mm. of mercury, or both, then 51 patients had hypertension before operation. Of these, 32 had normal and 19 continued to have raised blood pressure following operation. The persistence of hypertension after adrenalectomy did not necessarily indicate persistence of Cushing's syndrome for in 18 of the 19 patients in whom the blood pressure failed to become normal there was a remission or beginning remission of all the other signs and symptoms of Cushing's

Table V.—Blood Pressure in Cases of Cushing's Syndrome Associated with Adrenal Cortical Hyperplasia

Before operation		After operation	
Condition	Cases	Condition	Cases
Hypertension	51	Normal blood pressure	32
		Persistent hypertension	19
No hypertension	7	No hypertension	7

syndrome. It is presumed, therefore, that in these cases the hypertension was independent of adrenal cortical hyperfunction in its inception, or that the patient was left with irreversible vascular disease attributable to the previous adrenal cortical hyperfunction, or both. When hypertension persisted, the blood pressure after operation was usually lower than before operation and hypertensive retinopathy usually was improved. As a rule, myocardial function, if impaired before adrenalectomy, improved afterwards.

(2) *Glucose tolerance.*—This usually improved as other features of Cushing's syndrome regressed, and in some instances frank diabetes requiring administration of insulin disappeared completely.

(3) *Cutaneous pigmentation.*—13 patients had cutaneous melanosis of the type seen in Addison's disease. The pigmentation was usually associated with frank adrenal cortical insufficiency but this was not always so. The incidence of pigmentation has decreased since cortisone has been used as replacement therapy.

(4) *Changes in urinary 17-ketosteroids and urinary corticosteroids.*—Data on urinary 17-ketosteroids in a group of cases in which subtotal or total adrenalectomy was performed are shown in composite fashion in Fig. 1. Also included for comparison are data in 14 cases in which a tumour was found at operation and removed. The pre-operative values emphasize the impossibility of differentiating between tumour and hyperplasia in most cases on the basis of urinary 17-ketosteroids. Where the adrenalectomy was performed in two stages the reduction of 17-ketosteroids was not striking after resection of one hyperplastic adrenal gland. After resection of the second adrenal gland, the excretion of 17-ketosteroids in most cases reached low levels and in some instances remained low indefinitely or for

prolonged periods. Four high values found in 2 cases of tumour seven to ten months after operation were attributable to recurrence of malignant tumours.

Data on urinary corticosteroids (formaldehydogenic steroids) are shown in Fig. 2. Pre-operative values did not permit differentiation between tumour and hyperplasia. After resection or removal of one hyperplastic adrenal gland there was a trend toward lower values and in some cases the values became normal, but in many others they remained above normal. Following completion of adrenalectomy or excision of a tumour of the adrenal cortex practically all of the values were within the normal range or lower. Some of the post-operative values remained elevated to some extent owing to administration of cortisone which is excreted in part as a corticosteroid.

The described changes in excretion of steroids following adrenalectomy or removal of a tumour of the adrenal cortex are indicative of a pronounced reduction in the level of adrenal cortical function which was paralleled by remission of the signs and symptoms of Cushing's syndrome.

Comment

In severe form, Cushing's syndrome is a serious and progressive disease which, if untreated, carries an unfavourable prognosis. It appears, therefore, that radical surgical treatment is justified, as no other treatment in our hands, including roentgen irradiation of the pituitary gland, has afforded equally satisfactory results. 54 of the patients in the series reported herein in whom surgical exploration of the adrenal glands failed to reveal an adrenal cortical tumour were treated by subtotal adrenalectomy and 4 by total adrenalectomy. If the incidence of recurrences ultimately proves to be high after subtotal adrenalectomy, then total adrenalectomy may become the preferable form of surgical treatment.

The importance of surgical exploration of the adrenal glands to rule out tumour has been emphasized. In some instances the tumours are small and may not be detectable by other methods of examination.

The statements made here concerning the treatment of patients with Cushing's syndrome due to adrenal hyperplasia represent only present-day thought on this subject and may be changed in the future. Possibly non-surgical methods of treatment may be developed for patients in whom the presence of an adrenal cortical tumour has been excluded.

Summary

Cushing's syndrome may be produced by a functioning tumour of the adrenal cortex but more often it is a consequence of hyperplasia and hyperfunction of the adrenal cortices in the absence of tumour. Removal of the tumour or extensive resection of hyperplastic adrenal glands at present seems to be the treatment of choice. Important aspects of surgical treatment, including pre-operative and post-operative use of cortisone, have been outlined. To date, 54 patients with Cushing's syndrome caused by adrenal hyperplasia have been treated by subtotal adrenalectomy and 4 by total adrenalectomy at the Mayo Clinic. 46 of the 47 patients in this group who are living are at present in a state of satisfactory remission from Cushing's syndrome.

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Idiopathic Hypercalciuria

(A Preliminary Report)

By FULLER ALBRIGHT, M.D., PHILIP HENNEMAN, M.D., PATRICIA H. BENEDICT, M.D., and ANNE P. FORBES, M.D.

From the Stone Clinic of the Massachusetts General Hospital and the Department of Medicine, Harvard University Medical School, Boston, Massachusetts, U.S.A.

TWENTY-TWO patients are presented illustrating a syndrome characterized by a normal serum calcium level, a low serum phosphorus level, an increased urinary calcium excretion and, in most instances, a staphylococcal pyelonephritis, past or present. This dislocation of homeostasis

has been brought to our attention in the Kidney Stone Clinic of the Massachusetts General Hospital because of the frequency of kidney stones as a complication.

Flocks (1940) mentioned infection in the kidney substances and kidney pelvis as factors of importance in the formation of calcium stones in the urinary tract. He also noted high urinary calcium in a large group of individuals with renal stones; the exact cause of the hypercalciuria was undetermined. There are many known causes of hypercalciuria: hyperparathyroidism, hyperthyroidism, osteoporosis when the disease is progressing, high calcium intake, myeloma and metastatic malignancy, sarcoidosis, renal tubular acidosis, vitamin D poisoning, etc. It is the purpose of this paper, however, to point out a condition in which the cause of hypercalciuria is not as yet clear, hence the term "idiopathic hypercalciuria".

It will be noted at once that this syndrome has many features in common with hyperparathyroidism, notably low serum phosphorus, hypercalciuria and kidney stones. In fact the only distinguishing feature is the normal serum calcium level as opposed to the high serum calcium level in hyperparathyroidism. The serum calcium values of our 22 patients with idiopathic hypercalciuria were compared with serum calcium values in 14 cases of mild hyperparathyroidism. The hyperparathyroid patients were selected by taking the 14 cases, out of the series of 142 proven cases of the Massachusetts General Hospital series, which had complete data and had the lowest serum calcium levels. The range of serum calcium in this group was 10·2 mg./100 c.c. to 12·4 mg./100 c.c., with an average serum calcium value of 11·4 mg./100 c.c. It is thus evident that this group represents cases with a mild degree of hyperparathyroidism. Fig. 1 shows a comparison of the serum calcium, serum

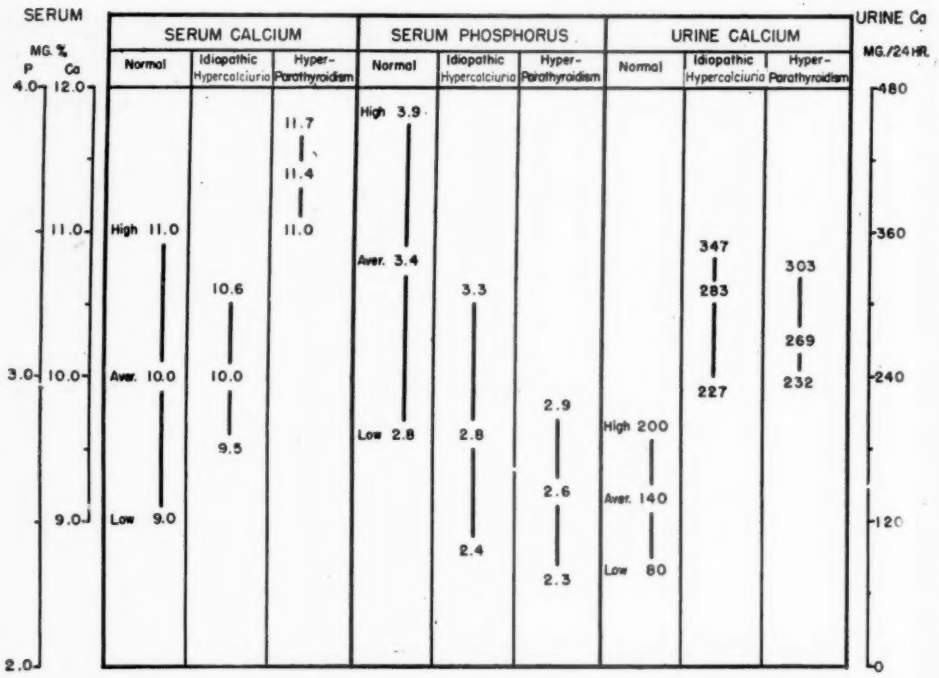

FIG. 1.—High, low and average values of serum calcium, serum phosphorus and urine calcium in normal individuals compared with similar values found in patients with idiopathic hypercalciuria and patients with mild hyperparathyroidism. The values for the latter two groups represent the average of all the high, low and average values for all the determinations recorded for that particular group of patients.

phosphorus, and urinary calcium in the normal, in the idiopathic hypercalciuria group and in the hyperparathyroid group. It is to be noted that in spite of the high values for serum calcium in the hyperparathyroid patients, the urinary calcium excretion is less in this group who have mild hyperparathyroidism than in the patients with idiopathic hypercalciuria; an average of 269 mg./24 hr. as compared with 283 mg./24 hr. (not statistically significant).

We have considered and ruled out hyperparathyroidism, even in mild degree, as an explanation of the high urine calcium in these patients. It might be thought, though there is nothing to suggest it, that a systemic acidosis with excretion of calcium as a base might explain the hypercalciuria. Accordingly, one of our patients with idiopathic hypercalciuria was given alkali while on a balance study, and the effects of this regime on urinary calcium studied. The patient was placed on a slightly

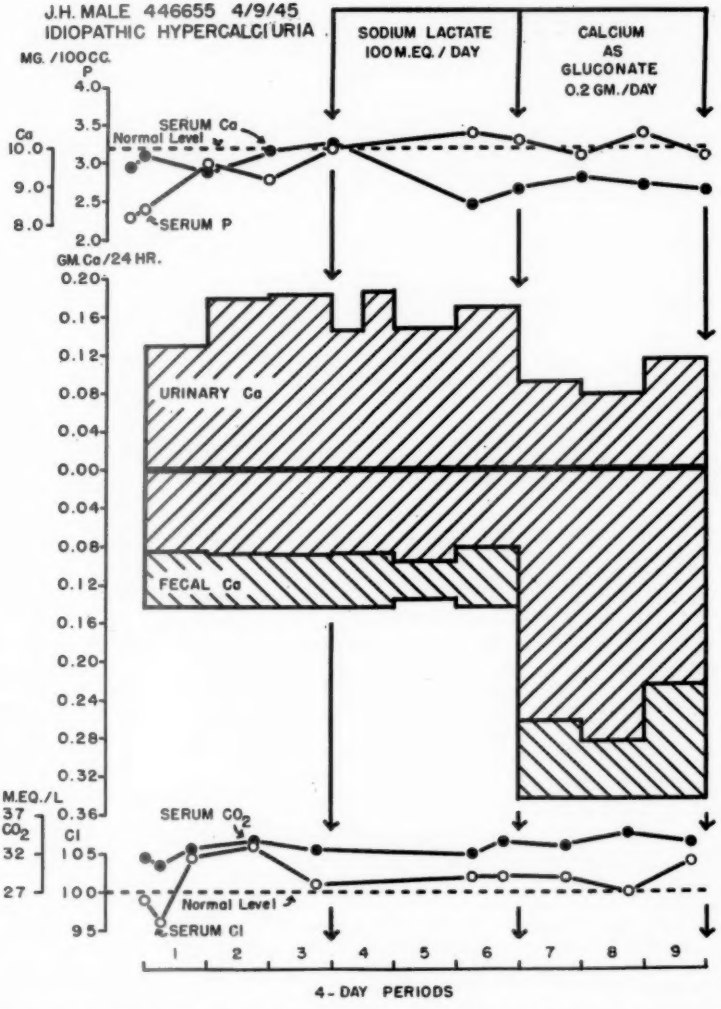

FIG. 2.—Studies on a patient with idiopathic hypercalciuria who received (1) sodium lactate and (2) calcium gluconate while on a slightly acid-ash diet. For discussion, *see* text.

acid-ash diet (about 70 m.eq./day) for three four-day periods; he was then given sodium lactate, 100 m.eq./day, the diet remaining unchanged. In the final three four-day periods, the 100 m.eq. of sodium lactate were replaced by 10 m.eq. of calcium as calcium gluconate. In Fig. 2 the high partition of calcium in the urine as compared with the fæcal calcium is to be noted. It will be seen that the calcium excretion in the urine, large to begin with, was not decreased by the sodium lactate therapy.

This is in marked contradistinction to what one finds in renal tubular acidosis where administration of sodium causes calcium to be saved and therefore decreased in the urine. (Albright *et al.*, 1940)

It is of interest to note the analyses of stones occurring in patients with idiopathic hypercalciuria and stone analyses in some other conditions associated with high urine calcium. Table I shows

TABLE I.—PHOSPHATE STONES

Table Showing Incidence of Renal Stones and Composition of Stones in Cases of Proved Hyperparathyroidism, Cases of Idiopathic Hypercalciuria, Renal Tubular Acidosis and Nondescript Cases of Nephrolithiasis

	Incidence	Number analysed	$NH_4 = 0$ Mg = 0
Hyperparathyroidism 142 cases ..	114 (80%)	36	75%
Idiopathic hypercalciuria	22 (100%)	14	79%
Renal tubular acidosis	7 (77%)	9	70%
Nondescript cases of nephrolithiasis ..	100 (100%)	100	38%

the incidence and analyses of renal stones in some patients with hyperparathyroidism, renal tubular acidosis, and idiopathic hypercalciuria, also 100 consecutive stone analyses in nondescript cases of nephrolithiasis are included. It will be seen that all of our 22 patients with idiopathic hypercalciuria had renal stones which proved on analysis to be calcium phosphate and/or oxalate with 79% negative for ammonium and magnesium. It is the experience of our clinic that stones of this composition have been formed in clinical states which are associated with high urine calcium and without urinary tract infection.[1]

It will be seen that in both hyperparathyroidism and renal tubular acidosis, conditions associated with high urinary calcium, the percentage of stones negative for ammonium and magnesium is also high whereas the percentage of stones negative for ammonium and magnesium in the nondescript cases of nephrolithiasis is very low. This suggests to us that the cause of the renal stones in idiopathic hypercalciuria may be the high urine calcium *per se*.

It was observed that these cases showed a high incidence of urinary tract infection. This might not seem surprising since renal stones are commonly associated with positive urine cultures of one or more organisms, although patients who have hyperparathyroidism with staghorn stones not uncommonly have sterile urine. Eighteen out of twenty-two of our cases showed *Staphylococcus albus* in one or more cultures. To be sure, this is a common contaminant in the male, and all our 22 cases were males. However, in many cases it was clearly the infecting organism. The question arises as to what might be the causal relationship between the urinary tract infection, the hypercalciuria and the renal stones. The authors suggest that the infection may possibly be the factor causing hypercalciuria.

That infection is certainly related to hypercalciuria seems evident in an instance of idiopathic hypercalciuria complicating idiopathic hypoparathyroidism. The patient has already been reported (Sutphin, Albright and McCune, 1943). He was followed for hypoparathyroidism for a period of years; he developed under observation acute staphylococcal pyelonephritis; this was associated with marked hypercalciuria (1,045 mg./24 hr.) in spite of the fact that his serum calcium was low; finally the hypercalciuria disappeared when the infection was cured by antibiotic therapy. With the high level of urinary calcium he quickly developed a kidney stone which had to be removed. The stone analysis was that which one expects with hypercalciuria (*see* above), namely, phosphate and oxalate with absence of ammonium and magnesium. The authors have seen several cases of hypercalciuria in patients with hypoparathyroidism and low serum calcium values in which there was no urinary infection. The mechanism of the hypercalciuria in these cases is quite different from that in the condition under discussion.

[1]We have used the presence of magnesium and ammonium in a stone as evidence of an infected, alkaline urine having been present at the time the stone was formed; conversely, absence of magnesium and ammonium in a phosphate stone is taken to be evidence of hypercalciuria having been present when the stone was formed. Of course there will be stones where the sequence of events was hypercalciuria→calcium phosphate stone→infection→alkaline urine→calcium phosphate-ammonium-magnesium stone.

We suggest the following sequence of events as a possible explanation of the hypercalciuria in these patients:

? Staphylococcal pyelonephritis
↓
? Renal tubular damage
↓
? Diminished tubular reabsorption of calcium
↓
HYPERCALCIURIA
↓
? Tendency to hypocalcæmia
↓
? Compensatory hyperparathyroidism
↓
? Hypophosphatæmia

The first attempts to find out what might be the disturbed physiology in this group of 22 patients have yielded no concrete explanation; the condition remains therefore, to us at least, *idiopathic* hypercalciuria.

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Klinefelter's Syndrome. Histo-Physiological Basis for a Pathogenic Interpretation

By F. A. DE LA BALZE, R. E. MANCINI, F. C. ARRILLAGA and J. IRAZÚ

III Catedra de Clinica Medica. Facultad de Medicina. Buenos Aires. Argentina

THE Klinefelter syndrome is a primarily testicular hypogonadism which apparently starts at puberty and involves all the elements of the testes. Patients are sterile and clinical manifestations of androgenic deficiency are not always noticeable. 8 cases have been studied by us, in which were found the clinical and hormonal characteristics described by other authors (Klinefelter *et al.*, 1942; Heller and Nelson, 1945; Nelson and Heller, 1945).

Morphological and histochemical studies of the testicular biopsy material have been made in order to obtain a histo-physiologic basis for a pathogenic interpretation.

Our histological findings in Klinefelter's syndrome (de la Balze *et al.*, 1952) are based on the comparison with the histological picture we have found in 16 normal adult testes (Mancini *et al.*, 1952) that we shall describe briefly:

(1) In the germinal epithelium an intense reaction for alkaline phosphatase is observed in all the cells; glycogen and general lipids exist in the spermatogonia and primary spermatocytes. Ascorbic acid exists occasionally in the primary spermatocytes. There are no glycoproteins or steroids present in the spermatic cells. In the Sertoli cells, lipids, glycogen and a slight reaction for alkaline phosphatase are found. Steroids are not observed. In the testes of older subjects, lipids increase and ascorbic acid appears in the Sertoli cells.

(2) In the wall of the seminiferous tubules there are glycoproteins in the basal membrane. The tunica propria shows acid mucopolysaccharides in the form of amorphous substance, a net of reticular

fibrils which thickens as it nears the basal membrane, and also rare elastic fibres. The fibroblasts of the tunica propria contain ascorbic acid, lipids, alkaline phosphatase and no steroids. These substances do not appear in the fibrocytes of the basal membrane.

(3) The intertubular connective tissue contains glycoproteins in the form of amorphous substance, rare collagenous fibres and a dense net of reticular fibres surrounding the Leydig cell groups. There are two types of Leydig cells: immature, without steroid but with alkaline phosphatase cytoplasmic basophilia and lipids, and mature or adult, with lipids, steroids, ascorbic acid, but without alkaline phosphatase and cytoplasmic basophilia. Free fibroblasts in the intertubular connective tissue contain lipids in general, and, at times, poor alkaline phosphatase and ascorbic acid reactions.

In the Klinefelter syndrome the following histochemical and morphological findings deserve attention: (i) Intertubular connective tissue alterations are as marked as tubular alterations. (ii) Most Leydig cells are shown by special methods to be abnormal and imperfectly developed; they have lost secretory activity and are in active proliferation. (iii) Early functional disturbance of the fibroblast of the tubule wall and the intertubular connective tissue. (iv) Loss of the normal morphological and histochemical features of the tunica propria and the basal membrane. (v) Few secretory Leydig cells are present; they are located near better preserved tubules.

The lesions of the intertubular connective tissue were as marked as those of the tubular wall and germinal epithelium. Clinically, however, sterility was always present, even when manifestations of androgenic deficiency were not apparent. As a result of the clinical, hormonal and special histologic studies on our cases, the following pathologic interpretation is proposed: at puberty a disturbance in the normal development and differentiation of the Leydig cells occurs so that few of them reach the adult secretory stage. This deficiency in androgenic action (particularly local action) causes abnormal fibroblast function in the tubular wall and in the intertubular connective tissue. Fibroblasts proliferate, produce abundant reticulin fibrils and, later, collagen fibres; finally hyalinization of the tubular wall occurs. The progressive lesion of the wall leads to atrophy of the germinal epithelium and Sertoli cells.

Our hypothesis is that the endogenous testosterone contributes through the fibroblasts to the development and maintenance of the seminiferous tubules, just as it maintains other elements of the male reproduction system.

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